

Is the evidence of the Supreme Court Ruling of gefitinib litigation in Japan scientific?

K. Katahira^{a,b,*}, T. Yoshikawa^b, H. Enoki^c, A. Teraoka^d and Y. Tsuchiya^e

^a*Faculty of Social Welfare, Niigata University of Health and Welfare, Niigata, Japan*

^b*Institute of Clinical and Social Pharmacy, Saitama, Japan*

^c*Postgraduate student of Niigata University of Health and Welfare, Niigata, Japan*

^d*Drug Information Center Asahi, Osaka, Japan*

^e*Graduate School of Human Science, Waseda University, Tokyo, Japan*

Received 10 March 2014

Accepted 18 August 2014

Abstract.

BACKGROUND: Plaintiffs of the gefitinib (Iressa) lawsuits in Japan started in 2004 were defeated in the Supreme Court in 2013. The Court judged it was not possible to foresee the outbreak of deaths caused by interstitial pneumonia due to gefitinib from death cases before approval of this drug.

OBJECTIVE: We attempted to verify validity of this judgment.

METHODS: We estimated the 95% confidence interval (CI) of the proportion of onset and death cases among 23 onset and 13 death cases occurring from “within 1 week” to “within 4 weeks” from clinical data before approval of this drug using data admitted to the Court.

RESULTS: For death cases, all of the upper limits of the 95% CI exceeded 50% within 1–4 weeks. This fact suggested that the cases of acute interstitial pneumonia were included in the clinical trial before the approval of gefitinib.

CONCLUSION: It was possible to foresee the outbreak of death cases after drug approval. This conclusion showed the Court’s ruling was not reasonable and was unscientific.

Keywords: Gefitinib, acute interstitial pneumonia (AIP), lawsuit, predictability, estimation

1. Introduction

Gefitinib (Iressa; AstraZeneca, London, UK) was first approved as an “effective” molecular-targeting agent indicated for the treatment of non-small-cell lung cancer in July 2002 in Japan. After starting sale of the drug, however, cases of lethal interstitial pneumonia (IP) as a serious adverse reaction (ADR) were reported one after another, resulting in 180 deaths before the end of 2002, when several safety measures were taken (Fig. 1).

* Address for correspondence: Kiyohiko Katahira, Director of the Institute of Clinical and Social Pharmacy, Misato, Saitama, Japan. Tel.: +81 48 955 7511; Fax: +81 48 955 7516; E-mail: katahirakiyohiko@gmail.com.

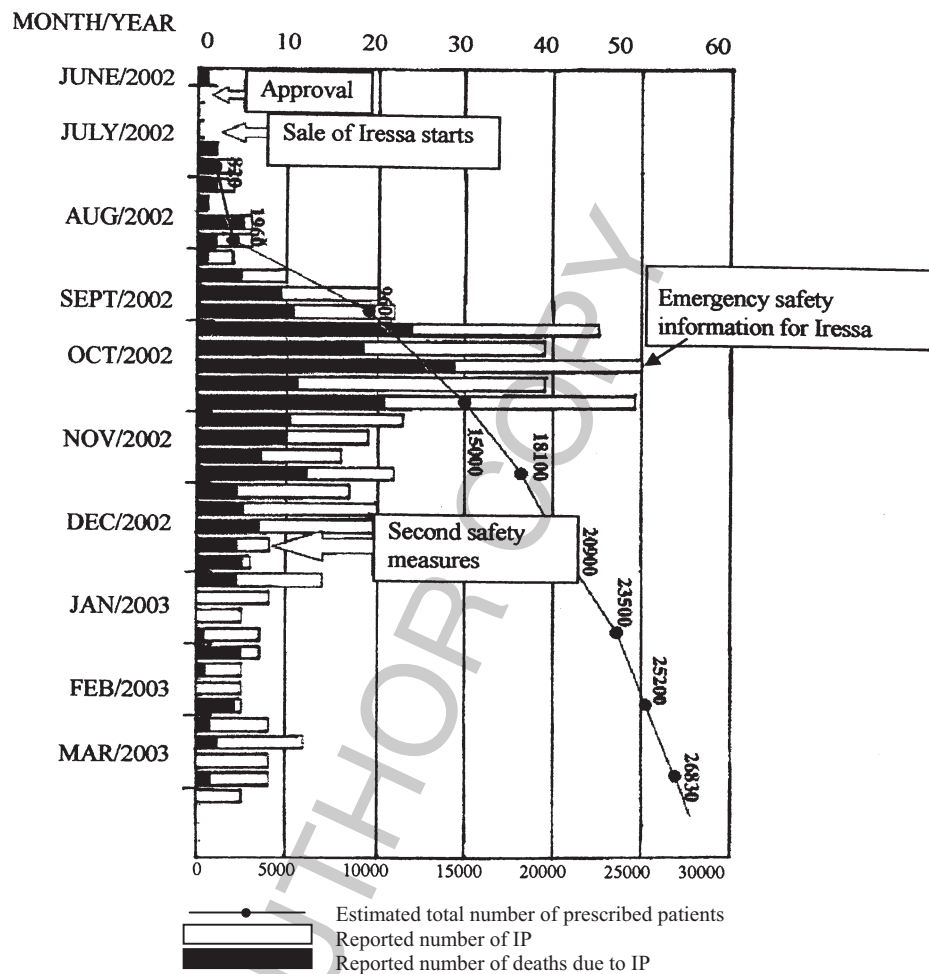


Fig. 1. Number of suspected cases of IP and deaths due to use of Iressa between June 2002 and March 2003 (source: Ministry of Health, Labour and Welfare of Japan).

In 2004, based on the Product Liability Law and Code of Civil Procedure, victims of ADRs brought upon taking Iressa filed lawsuits against AstraZeneca and the Japanese Government. The plaintiffs won in the Osaka District Court and Tokyo District Court (TDC) in 2011. However, they were defeated in trials in the Tokyo (in 2011) and Osaka (in 2012) Higher Courts, and finally in the Supreme Court (President Justice: Itsuro Terada) in April 2013 [1].

One of the issues of the lawsuits was whether defendants fulfilled the duty of direction and warning of the risks of taking the drug. AstraZeneca did not warn of the lethality of IP due to Iressa by providing a warning section in the first and second editions of the package insert. The company wrote only that “IP may occur” in the column of “serious adverse reactions” on the second page (in a total of four pages) of the package insert. As shown in Fig. 1, the Company and Government warned of the lethality of IP due to Iressa through “Emergency Safety Information of Gefitinib” on 15 October 2002 because deaths due to IP occurred one after another since Iressa came on the market. One-hundred and eighty deaths of patients were reported until 25 December 2002, when the second safety measures (including revision of

the package insert, restriction of prescribed doctors, hospitalization of patients prescribed Iressa) were stated. The number of reported deaths has decreased since 25 December 2002.¹

In the Courts, defendants justified the description of IP in the column of “serious adverse reactions” of the package insert. They also insisted that physicians should have paid more attention because the lethality of IP was written in the medical literature published before July 2002. The Higher and Supreme Courts supported the defendants’ arguments. In our opinion, these arguments cannot explain the decrease in the number of death cases after taking safety measures twice in 2002 (Fig. 1).

2. Objective, methods and results

Another issue in the lawsuits was whether the postmarketing outbreak of death cases of IP could have been predicted before the approval of Iressa. In the definitive ruling, the Supreme Court judged it was not possible to foresee the outbreak of deaths due to IP after the approval of Iressa from death cases of reported ADRs in clinical trials and the extended access program (EAP) before approval based on the following description: “In the cases of occurrence of interstitial pneumonia reported in the abovementioned clinical trials and in the EAP side effects information, the period after the administration of Iressa until the occurrence of the disease was 2 to 148 days, and in the death cases in which the causal relationship between the administration of Iressa and the patient’s death cannot be denied, the period after the occurrence of the disease until the patient’s death was 0 to 30 days. Thus, all of these cases did not imply that Iressa could cause interstitial pneumonia as its side effect which would occur at an early stage and progress rapidly.” [2]. In relation to this judgment, the concurring opinions by Justice Otani Takehiko and Justice Ohashi Masaharu were: “As explained in the court opinion, Iressa has a side effect of causing interstitial pneumonia that becomes severe rapidly, and it was impossible to foresee such a side effect from clinical trials conducted before the Approval for Import was granted” [3]. We found the same numbers (except one; 167 days, see below) in the ruling of the TDC [4]. The TDC examined each reported ADR case in detail and concluded that the number of days between starting administration of Iressa and onset of IP admitted by the TDC (23 cases in total) were: 2, 10, 12, 12, 13, 15, 16, 20, 21, 26, 26, 40, 40, 48, 48, 51, 53, 53, 68, 82, 86, 148 and 167. (Note: as mentioned above, we added 167, thinking that it was probably an error of citation by the Supreme Court.) The mean \pm SD value was 46.0 ± 42.2 days. The number of days between onset of IP and death (13 cases in total) was: 0, 4, 5, 7, 7, 8, 9, 11, 11, 18, 20, 21 and 30. The mean \pm SD value was 11.6 ± 8.4 days.

From these data, we calculated the proportions of onset cases and death cases among 23 onset cases and 13 death cases from “within 1 week” to “within 4 weeks”, respectively. We named this proportion the “premarketing proportion”. Then, we estimated the 95% confidence interval (CI) of the population from this premarketing proportion (Table 1).

Summarizing the results of the estimation mentioned above, the upper limits of the 95% CI of the premarketing proportion exceeded 50% within 3–4 weeks for the proportion of onset cases. With regard to the proportion of death cases, all of the same estimated number exceeded 50% within 1–4 weeks. The 95% CI of average days of death was 3.5–19.7 days.

¹The number of reported deaths due to ADRs because of Iressa administration has declined gradually since 2004, resulting in ≤ 10 deaths since 2005. The number of death cases, however, was reported until at least January 2014. According to MHLW, the total number of them was 891 as of January 2014. We consider the countermeasures for Iressa in the USA to be appropriate because the drug was forbidden in principle for new patients in June 2005 and because AstraZeneca withdrew approval of a new drug application for Iressa in 2011. The Food and Drug Administration noted this fact in the Federal Register on 25 April 2012.

Table 1

Ninety-five percent confidence interval (95% CI) of proportions of onset and death of IP estimated from premarketing proportions of serious ADRs of Iressa within 1–4 weeks (postmarketing proportion was added after estimation; 95% CI was calculated using the F-distribution because the sample size was small)

	Premarketing proportion of onset cases	95% CI		Postmarketing proportion of onset cases
		Lower limit	Upper limit	
<i>Proportion of onset cases</i>				
Within 1 week	1/23 (4.3%)	0.1%	21.9%	10/46 (21.7%)
Within 2 weeks	5/23 (21.7%)	7.5%	43.7%	18/46 (39.1%)
Within 3 weeks	9/23 (39.1%)	19.7%	61.5%	26/46 (56.5%)
Within 4 weeks	11/23 (47.8%)	26.8%	69.4%	29/46 (63.0%)
<i>Proportion of death cases</i>				
Within 1 week	5/13 (38.5%)	13.9%	68.4%	12/24 (50.0%)
Within 2 weeks	9/13 (69.2%)	38.6%	90.9%	17/24 (70.8%)
Within 3 weeks	12/13 (92.3%)	64.0%	99.8%	19/24 (79.2%)
Within 4 weeks	12/13 (92.3%)	64.0%	99.8%	22/24 (91.7%)

In addition to the estimated numbers, we introduced the two patients presented to the TDC by AstraZeneca and the Ministry of Health, Labour and Welfare (MHLW). Progression from Iressa administration to the onset of IP and death could be noted clearly. For both patients, the period from IP onset to death was < 3 weeks. It was not denied by the TDC and Supreme Court that the cause of death was IP by Iressa administration.

2.1. Case 1

A 73-year-old female was enrolled in the EAP with ZD1839 (Iressa) for patients with advanced non-small-cell lung cancer on 7 February 2002. On 1 April 2002 (53 days after beginning Iressa administration), the patient was hospitalized because the chest radiograph showed diffuse interstitial pulmonary infiltration. The patient experienced severe dyspnea and dry cough (slight to severe) and hypoxemia. The lung biopsy suggested reactive pneumonia and was suspected to be due to a certain medication. Bacteria, fungi or viruses were not found upon biological testing. On 2 April 2002, the patient began to be treated with high-dose corticosteroids, but apnea began and she was rushed to the intensive care unit. On 12 April 2002 (11 days after onset of IP), she died. The physician in charge stated that the cause of death was related to ZD1839 [5]. The TDC stated that the cause of death was IP due to Iressa administration.

2.2. Case 2

Case 2 was a 73-year-old Japanese male with non-small-cell lung cancer diagnosed in April 2001. He was administered Iressa after importing the drug personally from outside Japan. He started to take the drug on 29 March 2002 and experienced diarrhea, vomiting and pyrexia. The drug was stopped because of pyrexia. Subsequently, dyspnea appeared upon exertion. On 16 May, he entered hospital. He was admitted because diffuse shadows on both lungs were observed upon chest radiography. Despite steroid pulse therapy, administration of antibiotics and supplemental oxygen, his condition worsened. On 22

May, sedatives were started because he experienced severe dyspnea. On 24 May, he died because of respiratory failure owing to pneumonia. Autopsy limited to the left lung was done, but the results were not revealed [6]. The TDC stated that the cause of death was IP due to Iressa administration.

3. Discussion

(a) Brief history of identification and definition of acute interstitial pneumonia (AIP) before January 2002

In 1935 [7] and again in 1944 [8], Hamman and Rich described four unusual cases of idiopathic pulmonary fibrosis with an acute, fatal course and with distinctive histopathologic changes in lungs at necropsy. In 1969, Parr classified three similar cases as having the “Hamman–Rich syndrome” [9].

In 1986, Katzenstein et al. [10]. proposed that similar cases that developed the disease at early stages and died (5 out of 8 cases died 23–60 days after disease onset) should be distinguished from chronic interstitial pneumonia and be defined as AIP.

In 1991 [11], the Research Committee on Diffuse Lung Disease of Health and Welfare of Japan classified idiopathic IP into two types: acute and chronic.

In May 2000 [12], a symposium on Clinical Topics in Pulmonary Medicine was held in Toronto, Canada, in which Brown K.K. of Denver reported on AIP and Fitzgerald J.E. of Dallas, TX reported on acute drug-induced interstitial pneumonitis.

In June 2001, a Joint Statement from the American Thoracic Society (ATS) and European Respiratory Society (ERS) was adopted as the International Multidisciplinary Consensus Classification of Idiopathic Interstitial Pneumonias. In this literature, the clinical course of AIP was described: “There is no proven treatment and mortality rates are high ($\geq 50\%$), most deaths occurring between 1 and 2 months of illness onset” [13]. This literature was published in January 2002 [13], more than 5 months before Iressa was authorized for marketing by the MHLW in Japan. Officials in the MHLW in charge of approving Iressa and AstraZeneca should have been aware of this literature. They could have suspected that a death case within a short period (e.g., 1 month) might have been due to AIP from reading this literature as well as serial reports of adverse events of IP observed in clinical trials (including the EAP for Iressa). If officials responsible for patient safety were not aware of such literature, this may suggest negligence on their part.

(b) Did AIP cases include in the 13 death cases reported before authorization of Iressa in Japan?

As mentioned above, if we focus on the days from disease onset to death of these cases, all 13 cases died < 1 month after administration of Iressa. The causal relationship between death and Iressa administration cannot be denied. The 95% CI of average days of death was 3.5–19.7 days, i.e., within 1 month.

Important issues are clinical course and the outcome of these death cases (including autopsy). However, autopsy was conducted for only one Japanese male (case 2 described above; a 73-year-old Japanese male named “TF”). For the other cases, autopsies were not undertaken and described merely as “autopsy not undertaken” in the case reports. Other symptoms such as “dyspnea” were noted in the case reports of case 1 and case 2, and had been introduced in consensus documents by ATS/ERS. The TDC judged that the cause of death for case 1 and case 2 was IP caused by Iressa. From these viewpoints, it cannot be denied that at least some cases of AIP due to Iressa were highly likely to be included in the 13 death cases. As described above, the Supreme Court mentioned a causal relationship between Iressa administration and patient death within 30 days after the onset of IP. This fact suggested that cases of AIP were included in

these 13 cases. Therefore, from the clinical data before the approval of Iressa, the outbreak of deaths due to IP could have been foreseen.²

(c) According to data published after authorization of Iressa, there was no significant difference in the number of days from disease onset to deaths between death cases before and after authorization of Iressa in Japan. In addition, the postmarketing proportion of onset and death cases from “within 1 week” to “within 4 weeks” was included within the 95% CI of the population predicted by cases before the approval of Iressa

The MHLW publicized 46 cases of IP (24 deaths and 22 severe cases) after the approval of Iressa [14]. For comparison of reported cases before and after approval of Iressa, we calculated the mean \pm SD values of average days between starting administration of Iressa and onset of IP, as well as between the onset of IP and death. The values were 28.2 ± 29.4 days and 11.9 ± 10.9 , respectively, and no significant difference was found between them ($p = 0.08$ and $p = 0.94$, respectively). Moreover, we calculated the proportion of IP onset and death from “within 1 week” to “within 4 weeks”, as mentioned in Table 1. As a result, all of the proportions of the 46 postmarketing onset cases and 24 death cases within 1–4 weeks were included within the 95% CI of the population predicted by cases before the approval of Iressa. These results showed that the postmarketing outbreak of IP owing to Iressa was not “out of prediction” but “within prediction”.

(d) Under current Japanese law, patients who experience and are harmed by adverse effects caused by anti-cancer drugs are not protected: Amendment of laws is necessary immediately

According to the Civil Proceedings Act of Japan, the errors of judgment described here mean that a retrial is not possible. Hence, the plaintiffs will have to abide by the final decision. In Japan, the Relief System for Sufferers from Adverse Drug Reactions was established after the subacute myelo-optico neuropathy (SMON) tragedy in 1980. However, the victims of ADRs after taking anti-cancer drugs are not eligible for this system. In this regard, three of the five judges mentioned the necessity of studying applications to this system for victims of anti-cancer drugs in the Supreme Court Ruling of Gefitinib Litigation. Amendment of this Act is necessary to enable correction of the “final judgment”.

(e) Accumulation and development of studies using statistical estimations to protect victims from adverse events from drugs are necessary.

In the future, to overcome the problem of “predictability” and/or preventing drug-induced suffering, we must organize additional studies using more precise data and conduct statistical analyses (including estimation). Such data are lacking in Japan at the moment.

4. Conclusion

From premarketing data, it was possible to foresee the outbreak of early death cases after the approval of Iressa. This conclusion showed the Court’s ruling was not reasonable and was unscientific.

Acknowledgments

We thank the lawyers of the Tokyo and Osaka Iressa Lawsuits for letting us see the documents exhibited in the courts. We also thank Dr. Rokuro Hama, Head of “Non Profit Organization Japan Institute of

²Inoue et al. of Tohoku University introduced 18 IP patients with non-small-cell lung cancer treated with gefitinib in the past 2 months. Among them, four have developed severe acute interstitial pneumonia. Inoue A, Saijo Y, Maemonde M et al. Severe acute interstitial pneumonia and gefitinib. *Lancet*, 361;137-39, 2003.

Pharmacovigilance (NPOJIP)” in Osaka, Professor Toshiya Sato of Kyoto University and Professor Shigenobu Aoki of Gunma University for their suggestions of the methods and interpretations of statistical estimation.

Conflict of interest

None of the authors have a conflict of interest.

References

- [1] The medical aspects and lessons of this problem were written in the following article: Nishimura T, Tada H, Nakagawa M, Teramukai S, Matsui S and Fukushima M. Lessons from gefitinib-induced interstitial lung disease in Japan: problems in approval, pharmacovigilance, and regulatory decision-making procedures. *Pharmacy Practice* (2006);4(4):168-178.
- [2] Supreme Court Judgment, 2012;293:8-9. Available from: <http://www.courts.go.jp/english/judgments/text/2013.04.12-2012.-Ju.No.293.html> Accessed December 30,2013
- [3] Supreme Court Judgment, 2012;293:20. Available from: <http://www.courts.go.jp/english/judgments/text/2013.04.12-2012.-Ju.No.293.html> Accessed December 30, 2013.
- [4] Tokyo District Court Judgment, (March 23, 2011) Available from: <http://iressabengodan.com/data/%E6%9D%B1%E4%BA%AC%E5%88%A4%E6%B1%BA%E7%AC%AC%EF%BC%93%E5%88%86%E5%86%8A%28%E3%83%9E%E3%82%B9%E3%82%AD%E3%83%B3%E3%82%B0%29%5B1%5D.pdf> (PART III, in Japanese) Accessed 2013.
- [5] AstraZeneca. Case report. Exhibited in court as Hei-B3-172-2. 2002.
- [6] AstraZeneca. Case report. Exhibited in court as Otsu-B14-1. 2002.
- [7] Hamman L, Rich AR. Fulminating diffuse interstitial fibrosis of the Lungs. *Tr.Am.Clin. & Climatol. A* 1935;51:154-163.
- [8] Hamman L, Rich AR. Acute diffuse interstitial fibrosis of the lungs. *Bull. Johns Hopkins Hosp.* 1944;74:177-212.
- [9] Parr LH. Hammon-rich syndrome idiopathic pulmonary interstitial fobrosis of the lung. *J of the Nat Med Assoc.* 1969;61(1):8-12.
- [10] Katzenstein A-LA, Myers JL, Mazur MT. Acute interstitial pneumonia: A clinicopathologic, ultrastructural, and cell kinetic study. *Am J. Surg. Pathol.* 1986;10(4):256-267.
- [11] Ando M. The concept and diagnosis criteria of idiopathic interstitial pneumonia. Ando M. Edited; *Pathophysiology and treatment of interstitial pneumonia. Results and Recent Trends of Research Committee of The Ministry of Health and Welfare of Japan.* 1996;121-127, *Shinryo-Shinsya.*
- [12] Nagai S, Izumi T. (supervised of translation): *Guideline of american thoracic society. Diagnosis and Treatment of Interstitial Pneumonias, Appendix3, 2003;144-145, Igaku-syoin.* (in Japanese)
- [13] Acute Interstitial Pneumonia. american thoracic society/European society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee. *Am J Respir Crit Care Med.* 165(2):292-294. Available from: <http://www.atsjournals.org/doi/pdf/10.1164/ajrccm.165.2.ats01>
- [14] Committee on the Safety Problem of Gefitinib. *Adverse Drug Reaction Reports of Interstitial Pneumonia/Acute Lung Injury by Gefitinib (Main Cases: 46). Material Number 11(December 25, 2002).* (in Japanese)