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Disproportionality Analysis of Osimertinib-related Adverse Events in Elderly Patients Using the Japanese Pharmacovigilance Database

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Abstract. *Background/Aim: Osimertinib is a well-tolerated first- or second-line treatment option for elderly patients with epidermal growth factor receptor mutation-positive advanced non-small cell lung cancer. However, the safety of osimertinib in elderly patients requires further investigation. Herein, we identified safety signals for various osimertinib-related adverse events (AEs) in elderly patients by disproportionality analysis using the Japanese Adverse Drug Event Report (JADER) database. Patients and Methods: Data from the JADER database from April 2004 to March 2023 were obtained from the Pharmaceuticals and Medical Devices Agency website. Safety signal detection for osimertinib-related AEs in elderly patients (≥70 years old) was determined using the relative elderly reporting odds ratio (ROR). For osimertinib-related AEs, we extracted 92 preferred terms (PTs) and nine standardized MedDRA queries (SMQs). Results: Safety signals in elderly patients were detected for "Cardiomyopathy (PT)" and "Cardiomyopathy (SMQ)". The symptoms most frequently associated with "Cardiomyopathy (SMQ)" included "Ejection fraction decreased (PT)", "Cardiomyopathy (PT)", and "Stress cardiomyopathy (PT)". Notably, 53.7% of these outcomes were "Recovery" or "Remission". The median time to the onset of "Cardiomyopathy (SMQ)" in elderly patients was 85 days (range=2-537 days). Conclusion: We demonstrated that patients ≥70 years potentially have increased osimertinib-related cardiomyopathy compared with patients <70 years. In the future, it is necessary to conduct research focusing on cardiomyopathy in elderly patients.*

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Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases and primarily affects the elderly (1, 2). However, despite its high incidence in the elderly, they are underrepresented in clinical trials, thus making it difficult to reach evidence-based clinical recommendations for these patients (2). The standard of care for patients with advanced NSCLC harboring epidermal growth factor receptor (EGFR) mutations is treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib, erlotinib, and osimertinib (3, 4).

Osimertinib, a third-generation EGFR-TKI, exhibits selective binding to EGFR driver mutations and EGFR T790M resistance mutations (5). In the FLAURA study, patients treated with osimertinib had a more favorable progression-free survival and overall survival than patients treated with first-generation EGFR-TKIs (4, 6). The 18-month survival rate was 83% with osimertinib *versus* 71% with first-generation EGFR-TKIs (4). In addition, fewer patients in the osimertinib group experienced grade 3 or higher adverse events (AEs) compared to the first-generation EGFR-TKI group (34% *vs.* 45%). Based on these results, osimertinib has been approved as the first-line treatment for EGFR mutation-positive NSCLC. However, only a small percentage (14.2%) of patients aged ≥75 years participated in the FLAURA study (4, 7). In prospective and retrospective studies, osimertinib demonstrated tolerability and potential as a first-line or second-line treatment option for elderly patients with EGFR mutation-positive advanced NSCLC (8-10); however, these studies had a small sample size, with only 38, 36 and 18

Table I. *Osimertinib-related adverse events*.

Category	Adverse event
PT	(>100 reports) "Interstitial lung disease", "Electrocardiogram QT prolonged", "Pneumonitis", "Lung disorder", "Cardiac failure", (10-99 reports) "Decreased appetite", "Pulmonary toxicity", "Diarrhea", "Platelet count decreased", "Drug resistance", "Liver disorder", "Hepatic function abnormal", "Cardiac failure congestive", "Malignant neoplasm progression", "Pleural effusion", "Erythema multiforme", "Thrombocytopenia", "Rash", "Neutrophil count decreased", "Pyrexia", "Metastases to central nervous system", "Deep vein thrombosis", "Acquired gene mutation", "Pulmonary embolism", "Nausea", "Anemia", "Malaise", "Drug eruption", "Ejection fraction decreased", "Pneumonia", "White blood cell count decreased", "Stevens-Johnson syndrome", "Death", "Pneumothorax", "Respiratory failure", "Pneumonia bacterial", "Cardiomyopathy", "Cerebral infarction", "Hyponatremia", "Blood creatine phosphokinase increased", "Renal impairment", "Dehydration", "Alanine aminotransferase increased", "Dyspnea", "Febrile neutropenia", "Aspartate aminotransferase increased", "Cardiac failure acute", "Myelosuppression", "Atrial fibrillation", "Metastases to lung", "Urticaria", "Long QT syndrome", "Stomatitis", "Metastases to meninges", "Paronychia", "Rhabdomyolysis", "Pneumonia aspiration", "Metastases to bone", "Pulmonary alveolar hemorrhage", "Vomiting", "Stress cardiomyopathy", "Metastases to liver", "Lymphangiosis carcinomatosa", (6-9 reports) "Cardiac dysfunction", "Hypokalemia", "Disseminated intravascular coagulation", "Skin disorder", "Drug-induced liver injury", "Eosinophilic pneumonia", "Enterocolitis", "Skin ulcer", "Cellulitis", "Cardiac failure chronic", "Carcinoembryonic antigen increased", "Acute kidney injury", "Ventricular tachycardia", "Hypoxia", "Fall", "Pulmonary hypertension", "Pancytopenia", "Gait disturbance", "Taste disorder", "Malignant pleural effusion", "Malignant transformation", "Hepatotoxicity", "Acute respiratory distress syndrome", "Acute myocardial infarction", "Vasculitis", "Blood alkaline phosphatase increased", "Myocardial infarction", "Pulmonary oedema", "Pulmonary artery thrombosis"
SMQ	"Torsade de pointes/QT prolongation 20000001", "Cardiac failure 20000004", "Cardiomyopathy 20000150", "Hematopoietic thrombocytopenia 20000031", "Hematopoietic erythropenia 20000029", "Hematopoietic cytopenias affecting more than one type of blood cell 20000028", "Interstitial lung disease 20000042", "Hematopoietic leukopenia 20000030", "Drug-related hepatic disorders - comprehensive search 20000006",

PT: Preferred term; SMQ: standardized MedDRA queries.

elderly patients enrolled, respectively. Therefore, additional studies with a larger cohort are necessary, particularly with respect to the safety of osimertinib in elderly patients.

The Japanese Adverse Drug Event Report (JADER) database of the Pharmaceuticals and Medical Devices Agency (PMDA) is a large spontaneous reporting system that reflects the realities of clinical practice in Japan. The JADER database and the reporting odds ratio (ROR) are used to analyze safety signal detection for AEs (11-13). The relative elderly ROR is used for safety signal detection in elderly patients defined by the European Medicines Agency (EMA) (14). For example, a previous study demonstrated that opioid-related AEs, such as respiratory depression, opioid-induced neurotoxicity, and akathisia, in patients ≥60 years old are potentially increased compared with those in patients <60 years old (11). Based on this result, we conducted an observational study, in which elderly patients were identified as a risk factor for opioid-induced neurotoxicity (a detected safety signal). Thus, the detection of safety signals for AEs contributes to determining the safety of pharmaceuticals. Herein, we identified safety signals for various osimertinib-related AEs in elderly patients using a disproportionality analysis of the JADER database.

Patients and Methods

Data source. The JADER database, sourced from the PMDA, encompasses data spanning from April 2004 to March 2023. This database consists of four tables: patient demographic information (DEMO), drug information (DRUG), adverse reactions (REAC), and primary disease (HIST). These tables are interlinked *via* a case ID. The DEMO table is cross-referenced with the DRUG, REAC, and HIST tables using this case ID. Elderly individuals are typically identified as those aged 65 and above. However, in the JADER database, the ages of patients are categorized in 10-year intervals (such as 10s, 20s, 30s). In previous studies of osimertinib, elderly patients were defined as ≥75 years old (8-10). Herein, we defined "elderly patients" as ≥70 years old and "younger patients" as <70 years old. We excluded patients for whom ages were unclear ("unknown", "adult", "elderly", "youth", "first trimester", "second trimester", "third trimester", "pediatric", "newborn", and "infant"). To avoid influence from the pediatric population, we excluded patients younger than 20 years. For the DRUG tables, the contribution of drug-related AEs was categorized as follows: "suspected drug", "concomitant drug", and "interaction". Our analysis solely focused on cases attributed to the "suspected drug" category.

Selection of data for osimertinib-related AEs. The AE names were characterized using the Medical Dictionary for Regulatory Activities/Japanese version 26.0 (MedDRA/J). For osimertinib-related AEs, 92 preferred terms (PTs) and nine standardized MedDRA

queries (SMQs) were extracted (Table I). We focused our analysis on PTs that appeared in six or more reports within the osimertinib cases. *Safety signal detection*. The ROR was derived through the utilization of two-by-two contingency tables as follows: a) the number of cases experiencing the specific AE after receiving osimertinib; b) the number of cases experiencing all other AEs after receiving osimertinib; c) the number of cases experiencing the specific AE after receiving other drugs; and d) the number of cases experiencing all other AEs after receiving other drugs. The safety signal was considered when the lower limit of the 95% confidence interval (CI) of the ROR exceeded one (11-13):

$$\mathrm{ROR} = \frac{a/c}{b/d}$$

Safety signal detection in elderly patients was determined utilizing the relative elderly ROR reported by the EMA (14). The relative elderly ROR was calculated as follows:

$$\text{Relative elderly ROR} = \frac{ROR_{elderly}}{ROR_{younger}}$$

The safety signal for elderly patients was identified when the lower limit of the 95%CI for both the $\mathrm{ROR}_{\mathrm{elderly}}$ and the relative elderly ROR exceeded one.

Analysis of "Cardiomyopathy (SMQ)". The JADER database contains information regarding patient outcomes after the occurrence of AEs. The outcomes of "Cardiomyopathy (SMQ)", for which safety signals were detected, were evaluated in elderly patients and classified into six categories as coded in the JADER database as "Recovered", "Remission", "Not recovered" "With sequelae", "Death", and "Unclear". We also determined the median duration and range of onset time for "Cardiomyopathy (SMQ)". Time to onset duration was calculated from the time of a patient's first prescription to the occurrence of "Cardiomyopathy (SMQ)". Only patients with complete AE occurrence and prescription initiation date information were included in the time-to-onset analyses.

Results

Number of osimertinib-related AE cases. The JADER database comprises 846,707 suspected drug cases from April 2004 to March 2023. After excluding patients with unclear ages and patients younger than 20 years, 709,937 cases (2,727 osimertinib and 707,210 non-osimertinib cases) were analyzed (Table II). Osimertinib cases were identified in 2,727, including 1,870 cases involving elderly patients and 857 cases involving younger patients. Non-osimertinib cases were identified in 707,210, including 314,836 cases involving elderly patients and 392,374 cases involving younger patients.

Relative elderly ROR of osimertinib-related AEs. Table III shows osimertinib-related AEs in which safety signals were detected in elderly patients. These included "Cardiomyopathy (PT)" (relative elderly ROR: 2.88, 95%CI=1.02-8.13) and "Cardiomyopathy (SMQ)" (relative elderly ROR: 2.05, 95%CI=1.06-3.95) (Table III). Except for these events, no PT or SMQ was detected that exceeded one for the lower limit of the 95%CI of the $\mathrm{ROR}_{\mathrm{elderly}}$ and relative elderly ROR.

Table II. *Number of cases analyzed*.

	Total	Elderly	Younger
Osimertinib cases	2,727	1,870	857
Non-osimertinib cases	707,210	314,836	392,374

Characterization of "Cardiomyopathy (SMQ)" in elderly patients. Figure 1 shows the ages of the 52 patients with osimertinib-related "Cardiomyopathy (SMQ)". About 76.9% of the patients were over 70 years old. Table IV lists the symptoms and outcomes of SMQ. Most of the symptoms of "Cardiomyopathy (SMQ)" included "Ejection fraction decreased (PT)", "Cardiomyopathy (PT)", and "Stress cardiomyopathy (PT)". The outcomes for "Cardiomyopathy (SMQ)" were "Recovered" or "Remission" in 53.7% of the cases. This was consistent even among elderly patients; however, 22.2% of cases had "Unclear" outcomes. Figure 2 shows the number of days from osimertinib administration to the onset of "Cardiomyopathy (SMQ)" in elderly patients. In total, 31 patients (including 32 symptoms) had data that included the date of initiation of osimertinib and the date of onset of "Cardiomyopathy (SMQ)". The median time to the onset of "Cardiomyopathy (SMQ)" in elderly patients was 85 days (range=2-537 days).

Discussion

To the best of our knowledge, this is the first study to analyze various safety signals for osimertinib in elderly patients using the JADER database along with RORs. Safety signals in elderly patients were detected for "Cardiomyopathy (PT)" and "Cardiomyopathy (SMQ)". The characteristics of SMQ were also identified. Most of the "Cardiomyopathy (SMQ)" symptoms included "Ejection fraction decreased (PT)", "Cardiomyopathy (PT)", and "Stress cardiomyopathy (PT)", whereas 53.7% of these outcomes were designated as "Recovered" or "Remission". The median time to the onset of "Cardiomyopathy (SMQ)" in elderly patients was 85 days (range=2-537 days). Consequently, our results have important implications for the management of elderly patients receiving osimertinib therapy.

Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2), causes reversible myocardial dysfunction through the inhibition of the HER2 signaling pathway (15). The HER2 plays an

Table III. *Disproportionality analysis of osimertinib-related adverse events.*

	Elderly patients		Younger patients		Relative elderly ROR	
	ROR	95%CI	ROR	95%CI	ROR	95%CI
Cardiomyopathy (PT)	11.75	6.82-20.23	4.08	1.69-9.86	2.88	1.02-8.13
Cardiomyopathy (SMQ)	9.59	6.95-13.23	4.68	2.64-8.3	2.05	1.06-3.95

PT: Preferred term; ROR: reporting odds ratio; SMQ: standardized MedDRA queries; CI: confidence interval.

important role in the development of the embryonic heart. Deletion of this gene in a preclinical mouse model results in early death (16, 17). The HER2 signaling in cardiac muscle cells is essential for preventing dilated cardiomyopathy (15). Similarly, osimertinib inhibits the HER2 signaling pathway (5, 18). Thus, HER2 may be involved in osimertinib-related cardiotoxicity, including cardiomyopathy. Moreover, elderly patients with breast cancer and a history of cardiac disease and/or diabetes treated with trastuzumab have an increased incidence of cardiotoxicity (19, 20).

In previous studies, osimertinib was shown to be an effective and safe treatment option for elderly patients with advanced NSCLC harboring an EGFR mutation (8-10). Cardiotoxicity, such as prolonged corrected QT interval and left ventricular systolic dysfunction, was observed in 5%-10% of cases in these studies; however, cardiomyopathy was not confirmed. Among the clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema, or decreased ejection fraction) occurred in 3% of the 1,479 osimertinib-treated patients, whereas 0.1% of the cardiomyopathy cases were fatal (21). Furthermore, osimertinib-related cardiomyopathy was reported in several post-marketing cases (18, 22, 23). Of note, the majority of these cases occurred in patients aged 70 or older. This study provides additional drug safety information regarding osimertinib treatment in elderly patients.

In general, the risk of AEs is higher in elderly patients than in younger patients because of increased comorbidity, polypharmacy, and inappropriate prescribing (24). Osimertinib is metabolized by CYP3A4; therefore, a risk of increased blood concentrations exists when co-administered with other drugs, particularly CYP3A4 inhibitors. By contrast, no clinically significant differences in the pharmacokinetics of osimertinib were observed based on age, sex, ethnicity, body weight, baseline albumin, line of therapy, smoking status, and renal or hepatic impairment (21). Thus, multiple factors may be associated with osimertinib-related cardiomyopathy in elderly patients.

To further characterize factors associated with cardiomyopathy, we calculated the time to the onset of

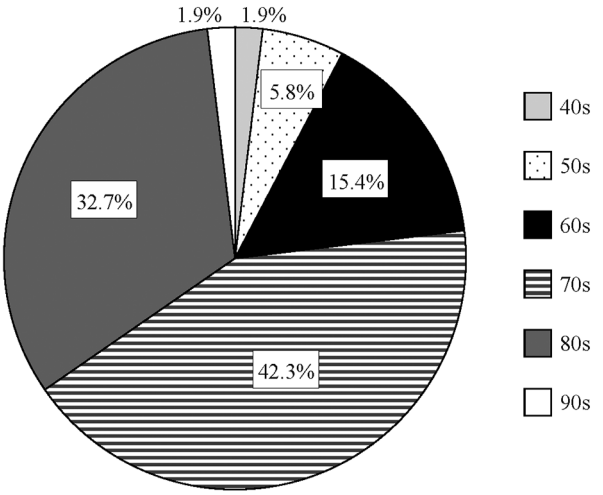

Figure 1. *Age of cardiomyopathy cases.*

cardiomyopathy in elderly patients. The results indicated that the time to the onset of cardiomyopathy greatly varied from a minimum of two days to a maximum of 537 days. In previous reports, the time to onset widely varied from 12 days to 72 weeks (22). Thus, the initiation of osimertinib in elderly patients may lead to cardiomyopathy at any time; therefore, their symptoms should be continuously monitored. In addition, this study provided information on the outcomes associated with cardiomyopathy. The outcomes were recorded as "Recovered" and "Remission" in 53.7% of the cases, with more favorable cases than deaths; however, 22.2% had an "Unclear" outcome. Previous case series revealed that osimertinib-related cardiomyopathy showed improvement in cardiac function with osimertinib discontinuation and with a cardioprotective approach (18, 22). Therefore, although caution is required in interpreting outcomes, this study has provided useful information for cases involving cardiomyopathy.

Study limitations. First, spontaneous reporting systems like the JADER database are susceptible to numerous biases,

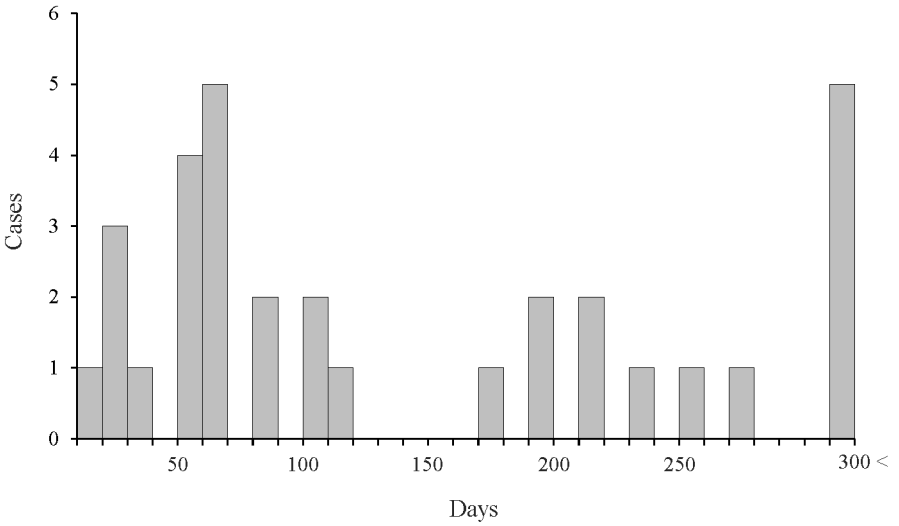

Figure 2. *Onset time of osimertinib-related cardiomyopathy.*

Table IV. Outcomes of osimertinib-related cardiomyopathy.

PTs		n	Recovered	Remission	Not recovered	With sequelae	Death	Unclear
All symptoms	Total	54	12 (22.2%)	17 (31.5%)	9 (16.7%)	1 (1.9%)	3 (5.6%)	12 (22.2%)
	Elderly	41	8 (19.5%)	14 (34.1%)	7 (17.1%)	1 (2.4%)	1 (2.4%)	10 (24.4%)
Ejection fraction decreased	Total	22	1 (4.5%)	5 (22.7%)	5 (22.7%)	1 (4.5%)	2 (9.1%)	8 (36.4%)
	Elderly	16	–	4 (25%)	5 (31.3%)	1 (6.3%)	–	6 (37.5%)
Cardiomyopathy	Total	19	5 (26.3%)	8 (42.1%)	3 (15.8%)	–	1 (5.3%)	2 (10.5%)
	Elderly	14	3 (21.4%)	6 (42.9%)	2 (14.3%)	–	1 (7.1%)	2 (14.3%)
Stress cardiomyopathy	Total	10	5 (50%)	4 (40%)	1 (10%)	–	–	–
	Elderly	8	4 (50%)	4 (50%)	–	–	–	–
Cardiotoxicity	Total	2	1 (50%)	–	–	–	–	1 (50%)
	Elderly	2	1 (50%)	–	–	–	–	1 (50%)
Tachycardia-induced cardiomyopathy	Total	1	–	–	–	–	–	1 (100%)
	Elderly	1	–	–	–	–	–	1 (100%)

PT: Preferred terms.

encompassing overreporting, underreporting, data omissions, and the absence of a denominator (11-13). Second, elderly patients with lung cancer are often defined as those over 75 years of age (8-10); however, the ages of patients registered in the JADER database are provided from data collected every 10 years. Therefore, we defined the elderly as those aged 70 years, rather than 75 years. Third, risk factors affecting cardiomyopathy and concomitant medications were not evaluated in the JADER database. However, this study is important in that it identifies potential new risks for the elderly patients receiving osimertinib using a large-scale real-world database. Finally, the ROR indicates an increased risk of AE reporting and is not a risk of AE occurrence (11).

Conclusion

To the best of our knowledge, this is the first study to identify various safety signals for osimertinib in elderly patients using the JADER database and RORs. We demonstrated that patients ≥70 years potentially have increased osimertinib-related cardiomyopathy compared with patients <70 years. In the future, conducting research focusing on cardiomyopathy in elderly patients is necessary.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

TO contributed to the study conception and design. Analysis was performed by TO with support from JA. The first draft of the manuscript was written by TO and all the Authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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