ARTICLE

Does Industry-Conducted All-Case Surveillance of Newly Approved Oncology Drugs Contribute to the Revision of Package Inserts in Japan?

Akiyuki Suzuki1,*, Hitoshi Sato1 and Yasutsuna Sasaki2,3

In Japan, the Pharmaceuticals and Medical Devices Agency requires all-case surveillance studies (ACSS) for many novel oncology drugs as a condition for approval. However, this is a major burden on the pharmaceutical industry and clinicians. The objective of this analysis was to investigate whether ACSS can contribute essential new information on severe adverse drug reactions, which are necessary to revise the package inserts of drugs. All oncology drugs for which ACSS were required from January 2006–September 2015 found on the Pharmaceuticals and Medical Devices Agency website were reviewed, and the influence of ACSS on the package insert content was evaluated. Most of the package insert revisions regarding serious treatment-related adverse events were based on spontaneous reports from clinicians. The contribution of ACSS results to the revision of package inserts is limited and comes at the cost of financial resources and labor. An alternative, more efficient adverse-event reporting system is necessary.

Cancer is the main cause of death in developed countries, including Japan. More than half of Japanese people are diagnosed with cancer in their lifetime, and the number of cancer deaths is still increasing.1 Since the beginning of the 21st century, many new types of oncology drugs, not only chemotherapeutics but also targeted drugs and immune checkpoint inhibitors, have been rapidly introduced and approved in Japan. However, a variety of nonhematological toxicities, including serious adverse drug reactions (ADRs), have been observed in patients who were treated with targeted drugs or immune checkpoint inhibitors.2,3 In addition, such kinds of serious ADRs are not fully reported before regular approval by a regulatory agency, and the accelerated approval system for oncology products also limits the information on serious ADRs in postmarketing settings.4,5

In 1993, the Pharmaceuticals and Medical Devices Agency (PMDA) and Ministry of Health, Labour and Welfare (MHLW) began to request industry-funded all-case surveillance studies (ACSS) for orphan drugs, such as anti-HIV drugs, as a precondition for approval, and required ACSS for irinotecan during the reexamination period as a condition for approval in 1995. ACSS are conducted in Japan to investigate safety and adverse events in all cancer patients to whom most newly approved oncology drugs were prescribed in postmarketing surveillance settings.6,7 There are several objectives of ACSS, including the prompt management of risk and the collection of information on ADRs, to determine the number of patients who use a drug and to understand the actual conditions of the usage of the drug in the real-world setting. According to an administrative communication, the

1Division of Pharmacokinetics and Pharmacodynamics, Department of Drug Information, Showa University School of Pharmacy, Tokyo, Japan; 2Division of Medical Oncology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; 3Oncology Center, Musashino Tokushukai Hospital, Tokyo, Japan.

*Correspondence: Akiyuki Suzuki (akiyuki.suzuki@gmail.com)

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ All-case surveillance studies (ACSS) are unique and large postmarketing surveillance studies that are conducted only in Japan; however, limited information is available as to whether ACSS actually provide essential and important information, especially with regard to the revision of package inserts.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ Do industry-conducted ACSS of newly approved oncology drugs contribute to the revision of package inserts in Japan?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
✔ The contribution of ACSS results to the revision of package inserts is limited and at a cost of financial and labor resources.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
✔ These results provide new insights into consideration of evaluation of adverse events based on real-world data in the postmarketing phase in Japan. An automated adverse-event reporting system is expected.
drugs for which ACSS are necessary are those that meet following conditions: (i) there are only a small number or no cases of domestic study subjects, and (ii) there are concerns about the drug regarding occurrence of serious ADRs. However, ACSS are a major burden on the pharmaceutical industry and on clinicians because eventually data on thousands of patients must be collected. The pharmaceutical industry must expend large resources, including a workforce.
and budget. Clinicians also must spend much time in completing case reports. The ACSS system is a unique and large postmarketing surveillance study system that is conducted only in Japan; however, limited information is available as to whether ACSS actually provide essential and important information, especially with regard to the revision of package inserts, at the cost of huge financial recourses and labor. The objective of this analysis was to investigate whether ACSS can contribute essential new information on severe ADRs that necessitates an addition to or a revision of package inserts of oncology drugs.

METHODS

Drugs for this analysis were selected based on the following criteria: (i) anticancer drugs, (ii) drugs approved in Japan with requirement of ACSS from January 2006–September 2015, and (iii) drugs for which the requirement of ACSS had been removed by September 2015. All approved anticancer drugs were selected, including cytotoxic drugs as well as targeted agents and immune checkpoint inhibitors based on a review of the PMDA website. The package inserts of these drugs were investigated, including the revision records and ACSS reports, to evaluate the influence of the results of ACSS on the revision of package inserts. When the revision records or the ACSS reports were not available, the respective pharmaceutical company in Japan was consulted directly.

Novel treatment-related adverse events (trAEs) added to a package insert based on ACSS were defined as follows: (i) the trAEs that were newly included in package inserts until removal of conditional approval of ACSS requirement, (ii) the trAEs that were observed in Japan if the information was available, and (iii) the trAEs that were newly reported in the ACSS if the lists of trAEs that were observed in ACSS were available. The removal date was defined as the date on which the description of ACSS as an approval condition was removed from the package insert. Clinically significant trAEs (CS-trAEs) were defined as trAEs that were included in the “Clinically Significant trAEs” section of the package insert. The data set was analyzed using descriptive statistics, including indication, approval date, planned and registered numbers of patients, study period, removal date, and final report issuance date.

RESULTS

During the surveillance period for this analysis, 147 anticancer drugs (as indication base) were approved on the basis of an PMDA/MHLW review. ACSS were requested by PMDA/MHLW for 52 indications of these drugs. The approval condition of ACSS was removed for 18 indications by September 2015, including 15 drugs that met the selection criteria (Table 1). The indications of these drugs covered not only rare cancers such as gastrointestinal stromal tumor and mantle cell lymphoma but also common cancers including colorectal cancer, non-small cell lung cancer, and breast cancer. The planned number of patients per ACSS ranged from 250–4,700. The relationships between the numbers of planned patients and the numbers of actually surveyed patients for safety analysis are shown in Table 1 and Figure 1. For most of the drugs, the number of patients for safety analysis was higher than the planned number of patients. In addition, actual ACSS surveillance durations varied widely, from 2.21–6.11 years (Table 1).

The revision of trAEs in package inserts based on ACSS is shown in Tables 2 and 3 and Figure 2. Median (minimum, maximum) of the number of novel trAEs that were included in package inserts based on ACSS was 7 (0, 32). For doxorubicin and carmustine, no novel trAEs from ACSS were included in the package inserts. Median (minimum, maximum) of the number of novel CS-trAEs that were added in package inserts based on ACSS was 1 (0, 21). The ACSS for doxorubicin, lapatinib, nab-paclitaxel, and carmustine provided no novel CS-trAEs to package inserts. The package inserts for only six (bortezomib, bevacizumab, erlotinib, cetuximab, panitumumab, and nab-paclitaxel) of the drugs included incidences of newly observed adverse events, but most of the trAEs and CS-trAEs were reported based on summary reports of ACSS but on spontaneous reporting by clinicians.

DISCUSSION

The occurrence of postmarketing ADRs is one of the most important public health problems worldwide. Especially for anticancer drugs, not only hematological toxicities but also nonhematological toxicities have become major concerns with both targeted agents and immune checkpoint inhibitors. Postmarketing surveillance for serious ADRs in many countries is primarily based on a spontaneous reporting system (SRS). However, whether a voluntary SRS can adequately reveal unreported serious ADRs is controversial. In contrast, the PMDA and MHLW require ACSS especially for selected newly approved drugs, such as...
Table 2. Reflection of novel clinically significant (CS) trAEs and novel trAEs to package insert from all-case surveillance studies

| General name | Package Insert Revision Date | Novel CS-trAE | Revised Category from NCS-trAE to CS-trAE | Novel NCS-trAE |
|--------------|-----------------------------|--------------|------------------------------------------|----------------|
| Bortezomib   | Ver. 4: Sept. 2008          | Ileus        | —                                        | —              |
|              | Ver. 5: Feb. 2010           | Reversible posterior leukoencephalopathy syndrome | — | — | Erythema multiforme, pruritis, impaired urination |
|              | Ver. 6: Sept. 2011<sup>a</sup> | Rem. of approval condition | — | — | Hypoglycemia, anxiety, faint, visual disturbance, extra systoles, tachycardia, atrial fibrillation, bradycardia, epistaxis, rhinorrhea, abdominal distension, esophageal reflux |
| Bevacizumab  | Ver. 6: Sept. 2009<sup>a</sup> | Interstitial pneumonia | — | — | Dizziness, parosmia, periodontitis, stomach discomfort, gastritis, gingival pains, glossitis, tooth loss, elevated fibrinogen, elevated INR, pruritis, urticaria, nail disorder, pain in extremities, arthritis, rhinorrhea, glucose urine present, increased CRP, injection site reactions, pneumonia, peripheral edema, complications associated with catheter (infections, inflammations, etc.), hot flush, infections, chest pain, cystitis, herpes zoster, infectious enteritis, increased y-GTP, increased FDP, rash |
|              | Ver. 8: Sept. 2010 Rem. of approval condition | — | — | — |
| Erlotinib    | Ver. 4: Jun. 2009           | Oculo-mucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, gastrointestinal perforation, corneal perforation | Corneal ulcer | Photosensitivity, skin pigmentation |
|              | Ver. 6: Sept. 2010<sup>a</sup> | Acute kidney injury, gastrointestinal ulceration, gastrointestinal hemorrhage | — | — | Skin fissures, skin ulcer, subcutaneous hemorrhage, skin vasculitis, eye pruritus, eye discharge, blurred vision, anemia, decreased platelet, dry mouth, gastritis, increased amylase, enterocolitis, esophagitis, heartburn, oropharyngeal pain, dizziness, increased blood pressure |
|              | Ver. 8: Feb. 2012 For NSCLC lift. approval condition | — | — | — |
|              | Ver. 11: Sept. 2013 | Severe skin disorder | — | — | Hand and foot syndrome | erythema, hematuria |
| Sorafenib    | Ver. 3: Dec. 2008           | Acute lung injury, interstitial pneumonia | — | — | — |
|              | Ver. 4: Apr. 2009           | Oculo-mucocutaneous syndrome (Stevens-Johnson syndrome) | Decreased white blood cell, neutropenia, lymphopenia, thrombocytopenia, anemia | Flushing, increased LDH, dysgeusia |
|              | Ver. 6: Sept. 2009          | Renal failure (including acute kidney injury) | — | — | Thyroid hyper function disorders |
|              | Ver. 7: Nov. 2009           | Hepatic failure, hepatic encephalopathy | — | — | Radiation recall reaction, hyperkalemia |
|              | Ver. 8: Oct. 2010           | Tumor hemorrhage, gastrointestinal ulceration, anaphylactic shock symptoms, rhabdomyolysis | — | — | Dizziness, edema |
|              | Ver. 9: May 2011            | Fulminant hepatitis, hemorrhagic enterocolitis, ischemic enterocolitis | — | — | — |
|              | Ver. 10: Apr. 2012          | Toxic epidermal necrolysis | — | — | Hypocalcemia |
|              | Ver. 11: Jun. 2012 For RCC Rem. of approval condition | — | — | — |
|              | Ver. 12: Mar. 2013          | Nephrotic syndrome, proteinuria | Hyponatremia | Hypokalemia |
|              | Ver. 15: Jun. 2015 For HCC Rem. of approval condition | — | — | — |
| Sunitinib    | Ver. 3: Sept. 2009          | Gastrointestinal fistulae, disseminated intravascular coagulation syndromes | — | — | Hypersensitivity |
|              | Ver. 5: Jan. 2011           | Cerebral hemorrhage, cerebral infarction | — | — | — |
|              | Ver. 6: Jul. 2011 Rem. of approval condition | Tumor lysis syndrome | — | — | — |
| General name | Package Insert Revision Date | Novel CS-trAE | Revised Category from NCS-trAE to CS-trAE | Novel NCS-trAE |
|-------------|-----------------------------|--------------|------------------------------------------|--------------|
| Cetuximab   | Ver. 2: Mar. 2010           | Heart failures, severe diarrhea | — | — |
|             | Ver. 4: Sept. 2012<sup>a</sup> Removal of approval condition | — | — | — |
|             | Ver. 5: Jan. 2011           | Tumor lysis syndrome | — | — |
|             | Ver. 7: Jul. 2012           | Peripheral arterial occlusive disease | — | Hyperkeratosis, oropharyngeal pain |
|             | Ver. 9: Apr. 2013           | Hyperglycemia | — | — |
|             | Ver. 10: Mar. 2014          | Cerebral infarction, transient ischemic attack | — | Hypertriglyceridemia |
|             | Removal of approval condition | — | — | — |
| Nilotinib   | Ver. 3: Jul. 2010           | — | — | Peripheral neuropathies, atrial fibrillation |
|             | Ver. 5: Oct. 2011           | Pulmonary arterial hypertension | — | — |
|             | Ver. 7: Mar. 2015           | Removal of approval condition | — | — |
|             | Ver. 5: Feb. 2014           | — | — | — |
|             | Ver. 5: Oct. 2013           | — | — | Gastrointestinal ulceration |
|             | Ver. 6: Sept. 2015          | — | — | — |
|             | Removal of approval condition | — | — | — |
| Dasatinib   | Ver. 2: Mar. 2011           | Renal failure, acute respiratory distress syndrome | — | Hypocalcaemia, increased blood bilirubin, nail disorder, acnes, arthralgia, proteinuria, increased γ-GTP, increased ALP |
|             | Ver. 3: Jul. 2012           | — | — | — |
|             | Ver. 5: Oct. 2011           | Pulmonary arterial hypertension | — | — |
|             | Ver. 7: Mar. 2015           | Removal of approval condition | — | — |
|             | Ver. 8: Jul. 2012           | — | — | — |
|             | Ver. 10: Mar. 2013<sup>a</sup> Removal of approval condition | — | — | — |
|             | Ver. 10: Mar. 2013<sup>a</sup> | — | — | — |
| Everolimus  | Ver. 2: Mar. 2011           | Renal failure, acute respiratory distress syndrome | — | Hypocalcaemia, increased blood bilirubin, nail disorder, acnes, arthralgia, proteinuria, increased γ-GTP, increased ALP |
|             | Ver. 3: Oct. 2012           | — | — | — |
|             | Ver. 5: Feb. 2014           | — | — | — |
|             | Ver. 6: Sept. 2015          | — | — | — |
|             | Removal of approval condition | — | — | — |
|             | Everolimus Ver. 2: Mar. 2011 | Renal failure, acute respiratory distress syndrome | — | Hypocalcaemia, increased blood bilirubin, nail disorder, acnes, arthralgia, proteinuria, increased γ-GTP, increased ALP |
|             | Ver. 3: Oct. 2012           | — | — | — |
|             | Ver. 5: Feb. 2014           | — | — | — |
|             | Ver. 6: Sept. 2015          | — | — | — |
|             | Removal of approval condition | — | — | — |
|             | Nab-Paclitaxel Ver. 3: Feb. 2013<sup>a</sup> Removal of approval condition | — | — | Hypoesthesia, muscle spasms, increased potassium, elevated bilirubin, decreased albumin<sup>a</sup> increased blood sugar |
|             | Ver. 2: Apr. 2012           | Hepatitis B | — | — |
|             | Ver. 3: Mar. 2013           | Removal of approval condition | — | — |
|             | Ver. 7: Sept. 2015          | Removal of approval condition | — | — |

*ALP, Alkaline phosphatase; AST, Aspartate amino transferase; CRP, C-reactive protein; CS-trAE, Clinically significant treatment related adverse event; FDP, Fibrinogen degradation products; GOT, Glutamic oxaloacetic transaminase; HCC, Hepatocellular carcinoma; INR, International normalized ratio; LDH, Lactate dehydrogenase; NCS-trAE, Non-clinically significant treatment related adverse event; PI, Package Insert; RCC, Renal cell carcinoma; trAE, Treatment-related adverse event; γ-GTP, γ-glutamyltransferase.

<sup>a</sup>Including numbers of incidence from ACSS in PI.
anticancer drugs. However, whether this system is working effectively or not remains unclear. According to the ACSS of cetuximab, the incidence and categories of ADRs were not distinct from previous reports.\textsuperscript{15}

In the present investigation, the package inserts for only 6 of the drugs included the incidence of newly observed adverse events out of 18 indications of these drugs and 15 drugs that met the selection criteria, but most of the trAEs and CS-trAEs were reported based not on summary reports of ACSS but on spontaneous reporting by clinicians. The contribution of the ACSS results to the revisions of package inserts is limited, although the framework of ACSS may promote clinicians to conduct intensive reporting of trAEs and CS-trAEs. The present investigation also shows that the incidence rates of both trAEs and CS-trAEs are valuable depending on the drug. In addition, the number of patients per ACSS required by the PMDA fluctuates widely, from 500 to thousands of patients, and is based on no clear rule. Not only the issue of ACSS or SRS but also the sample size of postmarketing surveillance is another important point to detect rare but CS-trAEs or life-threatening trAEs. The PMDA has become concerned about the induction of interstitial lung disease by targeting agents in Japanese cancer patients and has promoted conduction of ACSS.

Drug-induced interstitial lung disease was added to the Japanese package insert of sorafenib along with the issuance and distribution of “safety information for acute lung injury/interstitial pneumonia” after approval based on spontaneous reporting by clinicians.\textsuperscript{17} Because gefitinib was first approved in Japan for the treatment of non-small cell lung cancer in July 2002, the drug has been used in patients with non-small cell lung cancer. Shortly after the approval of gefitinib, however, it was recognized by many clinicians that the drug could cause severe, occasionally fatal, pulmonary damage and/or interstitial lung disease that could not be predicted during registration trials.\textsuperscript{18,19} The PMDA has become concerned about the induction of interstitial lung disease by targeting agents in Japanese cancer patients and has promoted conduction of ACSS.

### Table 3. Summary of trAEs and CS-trAEs from all-case surveillance studies for 15 drugs

| General name | Including numbers of incidence from ACSS | CS-trAEs | Revised category from NCS-trAE to CS-trAE | NCS-trAEs | Novel trAEs | Novel CS-trAEs |
|--------------|------------------------------------------|----------|-------------------------------------------|----------|-------------|---------------|
| Bortezomib   | Yes                                      | 2        | 1                                        | 15       | 17          | 3             |
| Bevacizumab  | Yes                                      | 1        | 0                                        | 31       | 32          | 1             |
| Erlotinib    | Yes                                      | 8        | 1                                        | 22       | 30          | 9             |
| Sorafenib    | No                                       | 15       | 6                                        | 10       | 25          | 21            |
| Sunitinib    | No                                       | 5        | 0                                        | 1        | 6           | 5             |
| Cetuximab    | Yes                                      | 2        | 0                                        | 0        | 2           | 2             |
| Nilotinib    | No                                       | 4        | 1                                        | 3        | 7           | 5             |
| Dasatinib    | No                                       | 1        | 0                                        | 2        | 3           | 1             |
| Doxorubicin  | No                                       | 0        | 0                                        | 0        | 0           | 0             |
| Lapatinib    | No                                       | 0        | 0                                        | 1        | 1           | 0             |
| Everolimus   | No                                       | 2        | 0                                        | 8        | 10          | 2             |
| Panitumumab  | Yes                                      | 0        | 1                                        | 11       | 11          | 1             |
| Nab-Paclitaxel| Yes                                      | 0        | 0                                        | 6        | 6           | 0             |
| Bendamustine | No                                       | 1        | 0                                        | 0        | 1           | 1             |
| Carmustine   | No                                       | 0        | 0                                        | 0        | 0           | 0             |

Yes: 6, No: 9 — — 7 (0, 32) 1 (0, 21)

Median (min, max) for number of trAE.

ACSS, All-case surveillance study, CS-trAE, Clinically significant treatment related adverse event, NCS-trAE, Non-clinically significant treatment related adverse event.
partially because the PMDA did not request ACSS for gefitinib just after approval.

Many serious ADRs may be discovered after a drug receives approval. This suggested a need for continued vigilance and efficient strategies for dissemination of information about ADRs associated with cancer drugs. Healthcare professionals may be more likely to report serious than nonserious adverse drug reactions. One reason a drug may be used for years before risks become evident may be that there is no active drug surveillance system. An automated reporting system is needed to obtain data for a database with an aim for re-vigilance and efficient strategies for dissemination of information about ADRs associated with cancer drugs. One of the pitfalls of the present analysis is that ACSS and SRS could not be compared directly; simulations for both postmarketing surveillance systems may contribute additional knowledge to this important issue. Another point is that most of the trAEs and CS-trAEs were reported by SRS on the basis of ACSS framework, and ACSS themselves could not be evaluated in those cases.

In conclusion, most of the revisions regarding serious trAEs in package inserts were based on spontaneous reports from clinicians. The contribution of the ACSS results to the revision of package inserts is limited, although the framework of ACSS may promote clinicians to conduct intensive reporting of trAEs and CS-trAEs. Future investigation is warranted to create an information-rich and cost-effective marketing surveillance system, especially for anticancer drugs.

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