LETTER TO THE EDITOR

Incidence of Severe Adverse Events Requiring Hospital Care after Trastuzumab Infusion for Metastatic Breast Cancer: A Nationwide Survey using an Administrative Claim Database

To the Editor:

Trastuzumab, a molecular targeted agent, has exhibited efficacy for HER2 (Human Epidermal Growth Factor Receptor Type-2) overexpressing metastatic breast cancer, in single usage or in combination with other anticancer agents (1). Today, trastuzumab infusion in outpatient chemotherapy clinics seems to be a common practice in patients with HER2-positive breast cancer in Japan. Outpatient chemotherapy is an integral part of the multidisciplinary approach to breast cancer treatment. A critical problem, however, should be acknowledged; a certain number of patients supposedly have severe complications following trastuzumab infusion. Several randomized clinical trials have indicated the incidence of mild-to-severe adverse events following trastuzumab infusion, including acute infusion reaction (2) and cardiac events (3,4). In a real-world clinical setting, however, it remains unclear how often clinic-based trastuzumab infusion results in subsequent hospitalization because of severe adverse events.

In the present study, we verified the incidence of trastuzumab-related adverse events that caused hospital admission followed by outpatient trastuzumab infusion, or increase in length of stay (≥3 days in hospital) among patients who underwent trastuzumab infusion during hospitalization, using the Diagnosis Procedure Combination (DPC) administrative claim database in Japan.

The DPC Inpatient Database includes information on patient backgrounds, date of admission and discharge, diagnoses coded with the International Classification of Diseases and Related Health Problems (Tenth Revision), drugs used, procedures, comorbidities at admission, and complications after admission. The DPC Outpatient Database includes data on date of visit, drugs used, and procedures performed at outpatient clinics. Data are collected during 6 months (from July 1 to December 31) every year. In 2007, data from around 3 million in patients were collected in the Inpatient Database, which represented approximately 45% of all acute care inpatient hospitalization in Japan (5). Given the anonymous nature of the data, the requirement for informed consent was waived. Study approval was obtained from our institutional review board.

A total of 43,297 trastuzumab infusions were performed for 3,181 patients with metastatic breast cancer at 394 oncology centers (56 teaching centers and 338 community centers) between July 1 and December 31, 2007. The average age (±SD) was 58.1 ± 9.3 years. In Japan, the standard protocol for trastuzumab injection for metastatic breast cancer is the first infusion at a loading dose of 4 mg/kg of body weight, followed by 2 mg/kg for weekly maintenance. Table 1 shows the rates of adverse events among all infusions (n = 43,297) when the data were divided into adverse events following the first trastuzumab infusion (4 mg/kg), and those following subsequent infusions (2 mg/kg). Among the 1,174 first infusions, 260 (22%) were performed in hospitals, and 914 (78%) in outpatient clinics. Among the subsequent 42,123 infusions, only 734 (1.8%) were performed in hospitals. The incidence of adverse events in all follow-up infusions (0.23%) was significantly lower than that in all the first infusions (0.60%; p = 0.024).

The list of trastuzumab-induced adverse events was made referring to the results of a previous randomized clinical trial (3). Among all the patients (n = 3,181), 105 (3.3%) patients had at least one trastuzumab-related complication; 59 patients had one complication, 23 had two, 15 had three, 4 had four, and 4 had...
five complications. Overall, a total of 186 complications were identified (shown in Table 2). Notably, 59 (1.9%) patients had diseases of the digestive system including emesis, 29 (0.91%) had infectious diseases including sepsis, 27 (0.85%) had respiratory diseases including pleural effusion and interstitial pulmonary disease, and 24 (0.75%) had diseases of the blood and blood-forming organs including agranulocytosis. Only 4 (0.13%) had heart diseases.

Table 3 shows the rate of adverse events among all infusions (n = 43,297) after data were divided into the different drug regimens used. Trastuzumab monotherapy was selected in 30,544 (71%) treatments. Trastuzumab combined with docetaxel caused a significantly higher incidence of severe adverse events than that of trastuzumab alone (0.97% versus 0.23%; p < 0.01).

Heart toxicity is a well-known risk of trastuzumab, and care must be taken in trastuzumab infusion to patients with heart disease (1,4). A previous randomized clinical trial showed that 0.6% of 1,678 women who underwent 1-year trastuzumab had severe congestive heart failure (New York Heart Association Class III or IV), 2% had a confirmed significant drop in left ventricular ejection fraction (LVEF) (3). By contrast, our study indicated that only 4 (0.13%) of 3,181 patients suffered from severe cardiac events requiring hospital care. A possible explanation of this relatively low incidence of severe cardiac events is that Japanese public insurance system allows frequent outpatient visit, which helps oncologists to identify early appearance of mild-to-moderate cardiac symptoms before it needs hospitalization.

The present study also showed that physicians in Japan tended to select trastuzumab monotherapy rather than a combination of trastuzumab and other anticancer agents. Randomized trials have elucidated that patients treated with chemotherapy should receive concurrent trastuzumab, but no study showed the

| Table 1. Adverse Events among 43,297 Infusions in Hospitals or Clinics Seen in the First Infusions or Infusions Thereafter |
|---------------------------------------------------------------|
| **First infusion (4 mg/kg)** | **Second and subsequent infusions (2 mg/kg)** | **Total** |
| n Adverse events | n Adverse events | n Adverse events |
| Hospitals | 260 3 1.2 | 734 12 1.6 | 994 15 1.5 |
| Clinics | 914 4 0.44 | 41,389 86 0.21 | 42,303 90 0.21 |
| Total | 1,174 7 0.60 | 42,123 98 0.23 | 43,297 105 0.24 |

| Table 2. Adverse Events Following Trastuzumab Infusion (n = 3,181) |
|---------------------------------------------------------------|
| Patients with at least one complication | 105 3.3 |
| Diseases of the digestive system | 59 1.9 |
| Emesis | 27 0.85 |
| Constipation | 17 0.53 |
| Diarrhea | 11 0.35 |
| Stomatitis | 3 0.09 |
| Ulcer of rectum | 1 0.03 |
| Infectious diseases | 29 0.91 |
| Sepsis | 6 0.19 |
| Acute pharyngitis | 4 0.13 |
| Acute tonsillitis | 2 0.06 |
| Acute laryngopharyngitis | 1 0.03 |
| Acute upper respiratory infection | 1 0.03 |
| Acute bronchitis | 5 0.16 |
| Herpes zoster | 3 0.09 |
| Mycosis | 2 0.06 |
| Pneumonia due to Pneumocystis carinii | 1 0.03 |
| Urinary tract infection | 3 0.09 |
| Acute cystitis | 1 0.03 |
| Diseases of the respiratory system | 27 0.85 |
| Pneumonia | 5 0.16 |
| Interstitial pulmonary disease | 6 0.19 |
| Pleural effusion | 14 0.44 |
| Respiratory failure | 2 0.06 |
| Diseases of the blood and blood-forming organs | 24 0.75 |
| Agranulocytosis | 20 0.63 |
| Anemia | 3 0.09 |
| Pancytopenia | 1 0.03 |
| Diseases of the skin and subcutaneous tissue | 14 0.44 |
| Ulcer of skin | 5 0.16 |
| Cellulitis | 4 0.13 |
| Eczema | 2 0.06 |
| Local infection of skin and subcutaneous tissue | 2 0.06 |
| Urticaria | 1 0.03 |
| Mental and behavioral disorders | 13 0.41 |
| Depressive episode | 2 0.06 |
| Dysthymia | 1 0.03 |
| Anxiety disorder | 2 0.06 |
| Sleep disorder | 8 0.25 |
| Diseases of the nervous system | 10 0.31 |
| Polyneuropathy | 4 0.13 |
| Dizziness | 5 0.16 |
| Coma | 1 0.03 |
| Heart diseases | 4 0.13 |
| Congestive heart failure | 2 0.06 |
| Atrial fibrillation | 1 0.03 |
| Other cardiac arrhythmia | 1 0.03 |
| Others | 5 0.16 |
| Phlebitis of lower extremities | 1 0.03 |
| Abnormal results of liver function studies | 4 0.13 |
Table 3. Adverse Events among 43,297 Infusions Using Trastuzumab Alone or in Combination with Anticancer Agents

|                    | n   | Adverse events | %   |
|--------------------|-----|----------------|-----|
| Trastuzumab alone  | 30,524 | 69              | 0.23 |
| Trastuzumab + paclitaxel | 6,718 | 10              | 0.15 |
| Trastuzumab + vinorelbine | 3,589 | 12              | 0.33 |
| Trastuzumab + capecitabine | 1,091 | 3               | 0.27 |
| Trastuzumab + docetaxel | 1,026 | 10              | 0.97 |
| Others             | 349  | 1               | 0.29 |

Conversely, that patients treated with trastuzumab should receive concurrent chemotherapy (2). The chemotherapy regimen should be chosen in accordance with the patient’s previous adjuvant therapy and coexisting conditions. The strategy of trastuzumab monotherapy can be justified because it appears to be effective for metastatic breast cancer and it surely avoids side effects observed with chemotherapy, possibly resulting in a better quality of life (6).

Several limitations of this study should be acknowledged. Studies using administrative claim data might be limited by incomplete reporting that could lead to overestimation or underestimation of complications. The DPC Outpatient Database lacks detailed information on patient backgrounds and precludes risk-adjusted analyses.

In conclusion, approximately 78% of the first trastuzumab infusions were performed in outpatient clinics. The rate of hospital admission following the clinic-based first infusions was 0.44%. This figure is substantially low, but not negligible. Recent advancements in controlling adverse events have enabled breast cancer patients to take chemotherapy in clinics. However, it should again be emphasized that careful follow-up is vital after trastuzumab infusion, particularly in outpatient clinics. Support from oncologists, trained nurses, and pharmacologists is essential. Systems should be established to deal with emergent events. Patients must be well informed on efficacy and safety of outpatient trastuzumab infusion. Our results can be utilized for informed decisions in breast cancer patients undergoing outpatient trastuzumab treatments.

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