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Utility of an adverse drug event database based on the narrative accounts of patients with breast cancer

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Summary **Patient narratives of adverse drug events (ADEs) often differ from the symptoms listed on the package inserts of pharmaceutical products using common ADE terminology and could be a source of great comfort to patients with the same disease. To explore this idea, we analyzed written narratives obtained from 48 patients with breast cancer using the NPO Corporation Database of Individual Patients' Experiences, Japan (DIPEx-Japan). Our analysis aimed to determine the utility of an "Adverse Drug Event Database" for use in clinical settings as a novel source of disease information in patients' own words. An analysis of transcripts from 29 patients, in which they recounted their treatment drugs and the time of onset and duration of ADEs in great detail, revealed several discrepancies between the language they used to describe various side effects and the standard ADE terminology on package inserts. We conclude that the language used to describe ADEs on package inserts is insufficient for helping patients as they struggle to recognize, internalize, and overcome ADEs, and argue the need for available, detailed information in the words of real patients about the nature of the ADEs predicted, as well as their clinical course and duration. Such information would be invaluable in supplementing the standardized language used on package inserts. Databases of patients' narrative accounts of ADEs are needed as information sources that can be reliably disseminated among patients.**

Keywords: Package inserts, qualitative research, ADE, DIPEx-Japan

1. Introduction

Information on adverse drug events (ADEs) used to be available only from papers published by corporations and medical professionals such as doctors and pharmacists. However, since 1993, when the US Food and Drug Administration instituted a program allowing patients to submit ADEs directly to the organization, similar patient ADE reporting systems have been introduced in various countries. Japan began testing its own patient ADE reporting system in March 2012 and the program is currently operational (*1*). Factors driving the introduction of ADE reporting systems include a tendency for doctors to fail to report ADEs, even when a patient's remarks strongly suggest an association with a treatment or drug (*2,3*), and a tendency for medical professionals to underestimate the degree and severity of ADEs (*4*). In addition, patients are often the first to discover side effects; certainly, they are the most sensitive to changes in their own bodies and their concern levels about these changes are the highest. Furthermore, their lack of expert-level knowledge about pharmaceuticals, paradoxically, better equips them to detect unknown and unforeseen events than medical professionals.

Nonetheless, the appropriate organization, analysis, and encoding of the vast amount of data collected in these ADE reporting systems remain to be addressed. In other words, the interpretation of the ADE-related information provided by patients with diverse

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backgrounds by medical professionals and government experts continues to be a challenge. Studies have cautioned that the risk of discrepancies arising in ADE data with respect to the symptoms actually experienced by patients is high, particularly at the encoding stage (*5,6*).

In recent years, these issues and concerns have driven research interest in so-called "patient-reported outcomes" (PROs), *i.e*., side effects as directly evaluated by patients, especially in cancer pharmacotherapy (*7*). ADEs are usually evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) (*8*). Corresponding guidelines, in the form of the *Patient-Reported Outcomes Version of the CTCAE* (PRO-CTCAE), have been developed and published for PROs (*9*). This assessment tool covers 124 labels across 78 different adverse events, describing their potential frequency, intensity, and impairment of daily living using standardized terminology.

Systematically collecting ADE-related information in a patient-centric fashion seems a useful idea. Pharmaceutical package inserts describe ADEs using standardized medical terminology; narrative accounts, in which side effects and symptoms may be expressed in quite different terms, could be a great help to people with the same disease. To examine this idea, we analyzed a database of patient narratives maintained by the NPO Corporation Database of Individual Patients' Experiences, Japan (DIPEx-Japan) (*10*); the database provides free, reliable information about health issues by sharing patients' real-life experiences.

DIPEx-Japan contains narrative clips (auditory clips and or video clips) and documents presenting the thoughts and feelings of patients with various diseases and their families in a wide variety of settings, such as during diagnosis, treatment selection, and treatment, as well as side effect experiences. One feature of the data is its high reliability; individuals' stories are collected with the approval of DIPEx-Japan's internal ethics committee and advisory council from the start of the project to online publication. In the present study, using DIPEx-Japan's "Breast Cancer Story Database" (*11*), we evaluated how patients with breast cancer's descriptions of side effects compared and contrasted with the official ADEs (and initial symptoms) listed on the package inserts of the medications they were taking, as well as how perceptions of the events varied among patients (*i.e*., in terms of the language used). We further assessed the utility of a hypothetical "Adverse Drug Event Database" for use in clinical settings as a novel source of disease information in breast cancer survivors' own words.

2. Methods

2.1. *Data used in analysis*

The original dataset consisted of narrative text data (*i.e*., transcripts) from survivors of breast and prostate cancer collected as part of A "*Patient Stories*" *Database for Cancer Survivors Aimed at Instituting a Support System to Allow Cancer Patients to Choose Treatments More Independently*," a 2007-2009 clinical cancer research project funded by Japan's Ministry of Health (Principal Investigator: Dr. Emiko Wada). Our analysis was confined to the transcripts of 48 patients with breast cancer.

Narrative content pertaining to adverse events or treatment was extracted and encoded into ADE categories (in patients' words). In addition to treatment history, the variables described below were encoded:

1. Patient ID: Internal identification number of the patient speaking about the side effect(s);

2. Adverse Events: Official ADEs listed on package insert(s) thought to match the patient's subjective symptoms;

3. Drug (Treatment): Name of the medication taken (or treatment received) by the patient at the time of subjective symptom onset (input as Unknown when uncertain);

4. Causality: Four-step rating of the causal link between the drug and the treatment received, according to the patient's description of their symptoms (Table S1, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=46*);

5. Listed on Package Insert: How well the side effects experienced corresponded to the actual descriptions of events in the drug or treatment in package insert; also rated on a four-step scale (Table S2, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=46*).

The Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (Japanese version) (*12*) was used to classify the potential adverse events listed on the package insert. Two researchers separately read and labeled the individual transcripts, indicating information which could be registered under these variables. The labels for which a consensus was reached were compiled into the final dataset.

We adopted several conventions for reporting the results. Drugs and medications are referred to using their standard terminology, but quotations are reported verbatim (*i.e.* in the patients' own words) and included in the tables. The quotations in the tables (Tables 1,2 Tables S3, S4, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=46*) are labeled with serial numbers corresponding to the 29 patients whose interviews were analyzed. In addition, since we did not analyze sentiment, interjections (*umm*, *wow*, *etc*.) that impeded reading were deleted, unless essential for context.

2.2. *Ethical considerations*

Our study was approved by the DIPEx-Japan Ethics

Committee (ID: 2012-1), on condition that we use only anonymized data from the original DIPEx-Japan database (*Story Archive*).

3. Results

The interviews conducted to construct DIPEx-Japan's *Story Archive* were not designed with the specific intention of obtaining information about chemotherapy. Nonetheless, our analysis of the narrative data revealed that 29 of the 48 patients with breast cancer spoke at great length about their treatment drugs, medication history, and the timing and presentation of their adverse events. Four had received pre-and post-operative chemotherapy and 16 had received postoperative radiation therapy as well. Moreover, "almost certain" causality was identified between drugs and events in 212 records. Tables S3 and S4 (*http://www.ddtjournal.com/action/getSupplementalData.php?ID=46*) contain representative excerpts of dialogue supporting drug-event causality with this high level of confidence (*i.e.*, causality ranked as "almost certain": see Table 2), in which the patient's language matched the description of the ADEs on the package insert of the drug or treatment in question. The varied language they used to describe their side effects provided a level of detail unknowable from the standard ADE terminology on package inserts. We present the remarks of patients taking paclitaxel concerning the side effect "paresthesia" as an example (Table 1).

However, in many cases, drug-event causality was not clearly evident from patients' narratives alone. Although we did not identify any "new" ADEs *per se*, several patients who had undergone combination chemotherapy (specifically, fluorouracil/epirubicin/cyclophosphamide [FEC or CEF], adriamycin/cyclophosphamide [AC], and trastuzumab/docetaxel [TRASTU/DTX] therapy) complained of hyperosmia (a heightened sense of smell), which was not listed among the potential reactions in their respective package inserts (Table 2). We searched a database of symptom reports associated with suspected ADEs published by the Pharmaceuticals and Medical Devices Agency, an independent administrative entity, for entries that resembled the patients' reports of

Table 1. Examples of characteristic narratives of patients with breast cancer concerning paresthesia induced by paclitaxel (or taxol)

No.	Narratives	Drug name
6	There was tingling [in my arms] from the wrists down [especially in my fingertips] … and from my lower knee down [in my legs]. The sensation was as if I had put my legs into an electric bath. I lose feeling in my legs when I sit seiza-style (*i.e. kneeling upright on the ground*). It feels like the sensation that you get when feeling starts to return to your leg after it's fallen asleep, but it started at the knee first, then spread downward. It doesn't go away, even when I try to sleep. At its worst, I just can't stay asleep, because the pins and needles wake me up after I've been lying down for about an hour.	Taxol
6	Let's say I rank how intense the tingling is from 0 to 10. From a starting point of 0, it would rise to a peak and then fall, but never back to 0, it would continue at 1. When I got my next [chemotherapy] shot, the tingling started at 1, then rose and fell again as if tracing a mountain. But this time it didn't go back to 1, it stayed at around 1.5 or 2 … My side effects multiplied like dust as the courses of chemo piled up. [The intensity] remained at around 2, even after four courses.	Taxol
8	My hands and feet got increasingly numb. It's been 31 months since my surgery, but my first finger joints on both hands, my fingertips, and the bottoms of my toes are still numb … When I got out of bed in the morning and planted my feet on the ground, there was this numb sensation, as if I were walking on top of something. I couldn't feel anything when I pushed down on the gas pedal when driving either. Gradually, I lost all feeling on the soles of my feet, from about the balls of my feet to the toes: it feels unpleasant. I can't feel anything when I walk barefoot on wooden flooring, either. [I have some] numbness in my fingertips. It's hard to keep a grip when I pour miso soup into a bowl, I feel like I'm going to drop something. I can't do tasks that require fine motor control of the fingers, or nerve feedback: it's difficult to open beer bottles, to put on a necklace, to press buttons, *etc*. It's like this constant tingling in the fingertips. [It] feels a little hot.	Paclitaxel
20	I felt that the numbness got worse quickly, even after finishing chemo. I started to have trouble doing various activities, and it became harder to, for example, pinch my fingers together. It's been 5 months since I finished chemo, but my hands and feet still feel numb, and my fingertips still hurt. [Always pins and needles.] I gradually lost feeling in my legs, from about my thighs down to my feet. Even today, I can barely feel the soles of my feet; [when I touch them,] it feels like someone is scratching them through rubber-soled boots. And yet when my feet bump into something, or someone steps on them, it's so painful I want to jump in the air.	Taxol (weekly)
20	I lost feeling [in my arms], [the numbness] gradually spreading from … the shoulder area down to my fingertips. My fingers too: I have a little trouble when I try to clench my hands very forcefully. I feel like I can't take the caps off bottles, pick up slender objects, do handicrafts, and so on.	Taxol (weekly)
24	My hands and feet would start tingling continuously. The numbness would continue for a while after I'd been sitting seiza-style, even after I started walking.	Taxol

Table 2. Examples of characteristic narratives of patients with breast cancer about a "heightened sense of smell"

No.	Narratives	Treatment
7	I became very sensitive to smells. This was a side effect of the chemotherapy; it was the worst for 3-4 days [after treatment]. I couldn't handle a lot of smells – the smell when the nurse went past, of her shampoo, of the toilet of the hospital – all of them bothered me.	FEC
12	On the third day, I really couldn't tolerate any odors, it felt like I was pregnant or something.	FEC
28	My sense of smell was inhuman, like an animal's. I couldn't tolerate the smell of the hospital, the smell of meals, the smell of tea. Smells were my arch-enemy, so much so that I wished for them all to disappear from the face of the earth. When you can't tolerate smells, you can't eat food. Thousands of times worse than morning sickness (*laughter*), thousands of times worse. I developed a keen sense of smell. Most of all, I don't know if it was the medicine, but I remember that I really stank afterwards.	AC
23	Conversely, I got increasingly sensitive to smell after the third round of chemo. [Whenever I wanted to eat something,] the first thing I did was to smell it. Sometimes it would smell delicious, sometimes it would smell a bit unappetizing. After I ate something, the smell leaving my nose would make me think, "Oh I like the way this smells", or "Maybe I don't."	TRASTU/ DTX

Table 3. Characteristic narratives of patients with breast cancer concerning information on adverse drug events

Category	Narratives
Information about rarely occurring adverse drug events	[Vascular pain] affects very, very few people who take [Pharmorubicin]. It's not listed as a potential side effect in the information sheet that the hospital gave me. I was surprised to experience this [wide] variation from person to person. Even [assuming an incidence of] 0.1%, I think you'd likely find quite a few people like me if you searched all of Japan. It took a year and a half before they figured out that I had developed interstitial pneumonia as a side effect of the hormone drug [I was taking]. I think there are others in the country who still don't know that it's [a potential side effect].
Reference material to determine whether side effects are reactions to chemotherapy, or symptoms of cancer progression	Xeloda's side effects were absolutely terrible. I started to wonder, "When I received preoperative chemotherapy [adriamycin+docetaxel], I was active enough to walk and go out almost every day: why do I feel so terrible now?" Was something about my own body causing this, rather than the drug? I felt that I couldn't tell what was the medicine's fault and what wasn't. For example, there are times when the chemo causes a bunch of side effects, and you think, "Is this a side effect? Or did the cancer spread?" It's very true, something starts hurting and you think, "Could this be cancer?" There was nowhere I could ask anyone about those kinds of things.
Information about side-effect severity, timing, duration, time profile, cure availability, and countermeasures	The instructions document did note numbness [as a side effect of] the weekly paclitaxel. But what was written there was like, please be careful not to trip and stumble. The information wasn't clear about the healing process either: how long it would take to get better, or the available treatments. If I just knew how long the side effects would last – the joint pain, the muscle pain, the red spots on my face – I could tolerate them.

olfactory disturbance. Although we could find none for the combination drugs FEC/CEF and AC, we noted three cases for TRASTU/DTX: one of hyposmia (2007) and two of parosmia (2011 and 2012) (*13*). Thus, the side effects spoken of by several patients had similar symptomology to that of anosmia. This ADE was likely omitted from the package inserts because of its extremely low incidence. However, our patients' stories suggest that it was indeed an adverse event to chemotherapy drugs, something we would not have known had it not been for their narrative accounts.

Some patients also noted a desire for detailed information about the potential side effects of chemotherapy, although they were few in number. They said that they wanted more information about rarely occurring ADEs, as well as their severity, timing, duration, time profile, cure availability, and countermeasures, and reference material to help them determine whether their side effects were reactions to chemotherapy or symptoms of cancer progression (Table 3). In addition, some patients learned about treatment efficacy and side effects via patient networking groups and internet blogs, as well as from the detailed instructions they received from nurses and pharmacists.

4. Discussion

Our analysis of narrative data from 29 breast cancer

survivors identified discrepancies between the ADEs listed on package inserts and the side effects described by the patients. We are aware of a variety of issues associated with our methodology. The study was not prospective: since interviewees had undergone different types of therapies and interview questions were not restricted to medication, their symptom narratives were likely affected by factors besides the drugs they were taking. These limitations notwithstanding, our study represents a novel attempt to extract information about drug events from individual patient dialogues in an existing database.

When planning this study, we predicted that patients' concerns about symptoms – *e.g*. "Does the side effect I'm experiencing now correspond to those in the medication's instructions?", "Am I the only one with this adverse event?", and "Is my condition getting worse?" – would not be adequately allayed by the bulk of the information provided today. We successfully identified discrepancies between the diverse array of symptomatic events described by patients and the incomplete descriptions on current package inserts.

Let us consider the language patients used to describe the side effect "paresthesia," an adverse event to paclitaxel mentioned by many patients. Interviewees described their symptoms using colorful and evocative language:

- *The sensation was as if I had put my legs into an electric bath*.
- *I couldn't feel anything when I pushed down on the gas pedal when driving either*.
- *Even today, I can barely feel the soles of my feet; [when I touch them,] it feels like someone is scratching them through rubber-soled boots. And yet when my feet bump into something, or someone steps on them, it's so painful I want to jump in the air*.

Readers can readily understand and/or determine the characteristics of the symptom paresthesia based on these patients' real-life experiences.

In addition, patients spoke in great detail about the various side effects they experienced:

1) Body parts
- *There was tingling [in my arms] from the wrists down [especially in my fingertips] … and from my lower knee down [in my legs]*.
- *Gradually, I lost all feeling in the soles of my feet, from about the balls of my feet to the toes*.
- *I gradually lost feeling in my legs, from about my thighs down to my feet*.

2) Conditions
- *… as if I had put my legs into an electric bath*.
- *I lose feeling in my legs when I sit seiza-style (i.e., kneeling upright on the ground). It felt like the sensation that you get when feeling starts to return to your leg after it's fallen asleep …*

3) Severity
- *From a starting point of 0, [the tingling] would rise to a peak and then fall, but never back to 0, it would continue at 1*.
- *My side effects multiplied like flies as the courses of chemo piled up. [The intensity] remained around 2, even after four courses*.

4) Duration
- *It's been 31 months since my surgery, but my first finger joints on both hands, my fingertips, and the bottoms of my toes are still numb*.

Paclitaxel package inserts describe adverse events using language such as "peripheral neuropathy, paralysis" and "hypoesthesia (peripheral neuropathy, such as paresthesia)." These descriptions lack information about the qualities of this "paresthesia," as well as its approximate onset and duration and the affected body part(s). One could thus expect many patients to be overwhelmed by anxiety, unable to foresee the exact side effects they should expect based on the language used in the current package inserts. In fact, a similar unease was apparent in the narratives of some patients when they relayed their feelings about the ADE information provided (Table 3). We conclude that the language used to describe ADEs on package inserts is insufficient to help patients as they struggle to recognize, internalize, and overcome drug-related side effects, especially in cancer chemotherapy settings. Detailed information in the words of real patients about the nature of the adverse events predicted, as well as their clinical course and duration, would have inestimable value in supplementing the standardized language used on package inserts.

Patient networking events, social networking services, and a variety of hospital-specific initiatives have separately been demonstrated as useful ways to gather information about individual patients. However, due to the risk of individual differences arising during data collection, we are convinced of the need to construct a database of patients' narrative accounts of ADEs as a source of information that can be reliably disseminated among patients.

We also discovered a variety of issues with our research methodology. Patient reflections were the source of the narrative data analyzed in this study. The interview structure was designed to allow participants to freely recount their personal experiences; it was not designed to investigate ADEs specifically. This made it challenging to identify the exact drug alluded to in many of the dialogues. Future studies will have the difficult task of determining causal links between different adverse events and individual medications. We believe that modifying the interview format to specifically obtain information about medications and ADEs is a necessary

step toward establishing clear causality between the drugs and their alleged side effects described in a narrative. This could be achieved by asking patients the name of their drug at the same time as asking them to describe their side effects and by checking which medications they have taken based on their medicine notebook and other sources.

Future efforts should add specific interview items that can clearly isolate events to drugs – *e.g.*, by establishing an independent line of questioning about chemo- and hormone therapy for about 10 min of the total interview – and identify and confirm with patients which medications they were actually taking using drug history handbooks and information packages. These new approaches could better explain the associations and gaps between patient narratives and the official ADEs described on package inserts.

Researchers of this topic should consider developing a specialized archive specific to adverse events to chemotherapy drugs, such as a hypothetical "Stories about Side Effects of Chemotherapy" database. With the assistance of patient caregivers (including family members) and medical professionals such as attending doctors, pharmacists, and nurses, this strategy could galvanize the construction of a highly accurate database, containing information about prescriptions, nursing care, drug history, and daily living environments. Furthermore, the utility of such a chemotherapy-specific archive for patients and related parties dealing with pharmacotherapy must be evaluated and validated. Jarernsiripornkul *et al*. reported that nervous and psychiatric symptoms and genital and breast diseases are over-represented in patient accounts of side effects (*3*). Similar trends could be present in patient narratives. When evaluating side effects based on patient accounts, researchers must base their analysis on the assumption that narrative information is different in many respects from the ADE reports of doctors and other professionals.

These limitations notwithstanding, we demonstrated that real patient accounts of medical treatment include copious amounts of valuable information that cannot be discovered from package inserts. Thus, an "Adverse Drug Event Database" could serve as a useful source of additional clinical information to supplement the formal, limited language on package inserts.

Conflict of interest

Kei Kikuchi, Noriko Iba, Rika Sato-Sakuma, Hirokuni Beppu: No conflicts of interest to disclose. Akiko Miki, Hiroki Satoh, Yasufumi Sawada: contributions from 10 companies in total, including five pharmaceutical companies: Shionogi & Company, Taisho Toyama Pharmaceutical, Dainippon Sumitomo Pharma, Mitsubishi Tanabe Pharma, and Nichi-Iko Pharmaceutical (AM: Project Lecturer, HS: Project Assistant Professor, YS: Project Professor). Yasufumi Sawada: Recipient of joint research funding from eight companies including Taiho Pharmaceutical, Dainippon Sumitomo Pharma, and Wakunaga Pharmaceutical.

Supplementary materials

This manuscript includes supplementary materials (electronic resources), available online.

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