Big Data and Pharmacovigilance: The Role of Oncology Nurses

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When new anticancer medications are approved, their safety profiles are often not fully understood. Oncology nurses have a responsibility to file reports of adverse drug events with safety registries such as MedWatch. If these registries receive prompt, complete, and accurate data from clinicians, agencies such as the U.S. Food and Drug Administration will have a stronger ability to detect hazards and to issue safety recommendations.

At a Glance
• In collaboration with physicians and pharmacists, oncology nurses have an obligation to contribute to national databases about medication safety. This is particularly important in the case of recently approved anticancer medications.
• Emerging systems allow patients to directly report symptoms and adverse effects.
• New techniques permit researchers to detect drug hazards by mining large-scale data from electronic health records and social media.

The U.S. Food and Drug Administration (FDA) has approved new antineoplastic medications at an increasing rate in recent years (Asabere & Bastian, 2015). The agency approved 19 novel cancer medications from May 2014 to December 2015, marking the fastest pace of approvals in roughly two decades (Amanam, Gardner, Young-Lin, & Chan, 2016). Many of these new agents seem promising—but history suggests that at least a few of them will turn out to carry safety hazards that were not adequately appreciated during clinical trials. As these novel medications are rolled out throughout the world, oncology nurses and other clinicians have an obligation to report significant effects and reactions to the drugs’ manufacturers and to national registries of adverse pharmaceutical events. (In the United States, the major registry is the FDA’s MedWatch system.)

However, clinicians’ reports to MedWatch are just one element of a high-quality pharmacovigilance program in oncology. Research during the past decade has demonstrated that incorporating patients’ own direct reports of their symptoms, not just clinicians’ reports, is important (Basch et al., 2014). Researchers also have begun to discover previously unrecognized adverse drug effects by mining data from electronic health records and from patients’ online behavior (White, Harpaz, Shah, DuMouchel, & Horvitz, 2014).

Complete, timely, and accurate drug event reports are extremely important, particularly during the first few years after a new medication has been approved. Consider the history of gemtuzumab ozogamicin (Mylotarg®), a monoclonal antibody that was approved in 2000 for the treatment of acute myeloid leukemia. During the preapproval clinical trials, veno-occlusive disease had been noted as a potential adverse effect. After the drug entered the open market, new evidence suggested that veno-occlusive disease was a more frequent event than the original trials had indicated (McKoy et al., 2007). The safety and effectiveness of gemtuzumab ozogamicin came under increasing scrutiny, and the drug’s manufacturer voluntarily withdrew it in 2010 (Richwine, 2010).

The gemtuzumab ozogamicin story suggests why maintaining accurate worldwide data sets about adverse effects associated with the newest antineoplastic medications will be vital. Programmed cell death protein 1 (PD-1) checkpoint inhibitors, such as nivolumab (Opdivo®), are proving to be extremely effective for certain patients with metastatic melanoma and a variety of other cancers (Rubin, 2015). At the same time, clinical trials of nivolumab found that patients sometimes suffered severe autoimmune reactions, including at least three fatal cases of pneumonitis (Topalian et al., 2014). As PD-1 checkpoint inhibitors enter widespread use in the marketplace, will the risk of severe autoimmune reactions turn out to
be lower, higher, or roughly the same as the risk that was found in preapproval trials? Timely and accurate reports from clinicians and patients will be essential in helping oncologists and oncology nurses employ these drugs safely.

Other challenges surround biosimilars, which tend to be approved on the basis of clinical trials that are much smaller than the trials required for wholly new medications (Camacho & Pai, 2015). Because the trials are smaller, they are less likely to detect rare adverse effects, which may become apparent only after the biosimilar product has reached the marketplace. In one well-known case, a certain biosimilar formulation of epoetin was found in post-approval studies to cause red cell aplasia—apparently because it used a different stabilizing agent than other versions of epoetin (Bennett et al., 2004).

**When and How to Report Adverse Events**

In collaboration with their physician and pharmacist colleagues, oncology nurses have a responsibility to ensure that their patients’ significant adverse drug events are properly reported. The procedure for filing reports varies between the preapproval and post-approval stages of drug development. During a clinical trial of an investigational drug, adverse reactions must be reported in accordance with the trial’s specific protocol. These reports are typically filed by the research nurses who coordinate the trial at each site. Bedside and chairside nurses who work with patients in clinical trials must ensure that their research nurse colleagues receive complete and accurate data about patients’ symptoms.

If the clinical trial is sponsored by the National Cancer Institute (NCI), adverse effects are reported through a structured system known as the Common Terminology Criteria for Adverse Events (CTCAE) (many industry-sponsored trials also choose to use the CTCAE). In recent years, scholars affiliated with the NCI have sought to expand the CTCAE system to include a component in which patients can directly report their own symptoms. This new component, known as the PRO-CTCAE™, may provide a more accurate and complete picture of patients’ reactions to medications (Basch et al., 2014).

After clinical trials are complete and a drug has won agency approval, the period of postmarketing surveillance begins. In the United States, nurses and other clinicians are encouraged to report significant adverse events to the FDA’s MedWatch database, which is more formally known as the Adverse Event Reporting System (AERS).

The FDA has sought to make filing AERS reports through MedWatch as simple as possible for nurses and other clinicians (Aschenbrenner, 2016; Miller, 2015). The agency has created an instructional website that includes nine case studies with detailed examples about how to file reports (FDA, 2013). The agency uses MedWatch reports to identify topics for further safety investigation. It also makes MedWatch data broadly available to scholars and the public.

Unfortunately, studies suggest that the vast majority of significant adverse events are not reported to MedWatch. For example, Moore and Bennett (2012) estimated that only about 2.5% of venous thromboembolisms associated with thalidomide were reported to MedWatch during a nine-year period from 1998–2006.

In addition, some research indicates that a large proportion of MedWatch reports are incomplete or inaccurate, making scholars and FDA officials detecting true signals about drugs’ safety more difficult. Getz, Stergiopoulos, and Kaitin (2014) found that 25% of clinicians’ MedWatch reports incorrectly named the medications in question, and that a majority of reports featured missing or inaccurate information about the date when the patient started the medication.

**The Importance of Patients’ Voices in Drug Surveillance**

A variety of studies have indicated that patients’ voices, not just those of clinicians, must be included in postmarketing drug surveillance. A team of Italian oncologists examined the experience of more than 1,000 patients with breast cancer or non-small cell lung cancer who were receiving chemotherapy (Di Maio et al., 2015). The study found that many of the patients’ self-reported toxicities were unreported by clinicians. Even when the patients reported “very much” toxicity, those toxicities were underreported by physicians at rates as high as 50%.

In a U.S. study of 163 patients with lung cancer who were receiving chemotherapy, Basch et al. (2009) found that patients’ self-reports of their symptoms provided more accurate portraits of their day-to-day health status than clinicians’ reports. By contrast, the clinicians’ symptom reports were more accurate than the patients’ reports in forecasting acute events, such as readmissions or emergency department visits (Basch et al., 2009).

A network of scholars has worked to create a common framework for patient-reported adverse outcomes, so that these reports can be meaningfully compared across many studies (Banerjee et al., 2013). This effort, which is known as the Patient-Reported Outcomes Measure Safety Event Reporting Consortium, has sought to define best practices in the collection and analysis of patient-generated reports. The FDA (2009) also has put forward its own guidance on the collection of patient-reported data.

**Mining Data**

Oncology nurses and other clinicians can mine information from the FDA’s MedWatch database to gain new insights about hazards associated with particular medications. For example, in one study, a team of oncology pharmacists combed through MedWatch reports for accidental overdoses of temozolomide (Temodar®), a medication with an unusually complex array of dosages and regimens (Lartare et al., 2014). Their analysis allowed them to detect specific patterns associated with overdose and to make recommendations about how to improve education for patients who have been placed on temozolomide therapy.

Scholars also have begun to experiment with data mining from electronic health records and social media content, as well as traditional registries such as MedWatch. Harpaz et al. (2013) analyzed MedWatch entries in combination...
with a database of more than 1 million narratives from electronic health records. Using this technique, the team detected an association between rash, buricase (Elitek®), a medication typically used to treat or prevent tumor lysis syndrome, and acute pancreatitis. Similarly, White et al. (2014) combined MedWatch data with large-scale data about patients’ online behavior, including their queries on Google and other search engines. They concluded that search logs can reliably be used to detect associations between medication and outcomes such as acute kidney injury or myocardial infarction.

Conclusion

Oncology nurses have several responsibilities associated with pharmacovigilance, particularly when their patients are using recently approved medications whose safety profiles are still not fully understood. Nurses should ensure that their physician and pharmacist colleagues receive complete, prompt, and accurate reports of patients’ symptoms. They should understand how to search the FDA database and other sources for emerging information about adverse effects. Finally, when they observe significant events that seem to be associated with a novel medication, they should file reports with MedWatch (or, if outside the United States, the relevant regional or national registry).

References