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EDITORIAL COMMENT

Potential and Pitfalls of Pharmacovigilance Databases in Oncology*

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The analysis of heart failure (HF) associated with human epidermal growth factor receptor 2 (HER2)-targeted agents by Wailiany et al[1] used the World Health Organization pharmacovigilance (VigiBase) database. This analysis compared the odds of HF between several cancer-directed regimens containing HER2-targeted therapies. A total of 78,028 patients from over 130 countries were included in the study. The analyses included patients who developed adverse drug reactions to monotherapy or combination therapies to either HER2-directed monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), or tyrosine kinase inhibitors (TKIs) with or without chemotherapy.

Pharmacovigilance aims to detect, assess, understand, and ultimately prevent treatment-related adverse events, and several large databases have been established.[2] Pharmacovigilance plays a role in monitoring patients receiving postmarketing treatment; data are collected in large surveillance databases, such as VigiBase. One of the major advantages of these databases is the number and diversity, at least geographically, of the patients who can be studied.

The authors used the reporting odds ratio (ROR) to determine the likelihood that a patient will develop HF with a specific treatment compared with patients receiving other therapies. The interpretation of the ROR has been controversial. Some have used it as a surrogate of the relative risk of an adverse reaction by analyzing the database as a case-control study in which patients who developed toxicity with a treatment are the cases, whereas patients with the toxicity and other treatments are used as the controls.[3] Others have suggested that given the limitations of pharmacovigilance databases, particularly the lack of a standard comparison group, they should only be used to determine if there is a signal in postmarketing studies to inform future research.[4] It is established that the ROR does not explain the incidence of a specific adverse reaction.[3,4] The information in the current study consists of patients with reported adverse drug reactions to HER2-directed therapies. The total number of treated patients or "population at risk" is not available; therefore, proportion measures describing incidences were not calculated in the study by Wailiany et al.[1,4]

In this study, a broad range of terms were used to identify potential cases of HF instead of using more standard criteria HF with or without reduced ejection fraction.[5] This was likely done to capture as many patients as possible; however, there are limitations of this approach. Terms such as "ischemic cardiomyopathy," "chronic left ventricular failure," and "stress cardiomyopathy" were included, and these would be atypical presentations for HER2-targeted therapy-induced cardiomyopathy. Therefore, it is possible that patients with other etiologies of cardiovascular disease were included as "cases." This is an important weakness of these databases, along with the lack of reporting of comorbidities and other risk factors.

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In this report, trastuzumab had the highest ROR (17.88) followed by ADCs (0.26) and TKIs (0.05).[1] Eleven percent of the reported patients receiving HER2-directed mAbs developed HF events; 2% of those were treated with ADCs, and <1% of patients were treated with TKIs.[1] The odds of developing HF on ADCs were much lower than with trastuzumab and consistent with what was previously reported (ie, incidence reported in clinical trials).[1,6] The majority of patients treated with ADCs in the current clinical practice have previously been treated with trastuzumab. Thus, there may be an ascertainment bias because they have already shown that they did not develop cardiotoxicity with trastuzumab therapy.

The authors' reported the low likelihood of developing HF with TKIs is consistent with prior studies; notably, echocardiographic monitoring of patients receiving TKIs is not widely recommended because of the limited evidence of HF.[1,7] It is possible that asymptomatic decreases in left ventricular ejection fraction (LVEF) in the TKI groups may have been under-reported in the present study. This study also showed that the use of TKIs (lapatinib and tucatinib) as monotherapy led to lower odds of HF than when combined with chemotherapy with or without trastuzumab.[7]

The present study showed that the odds of developing HF were higher in patients treated with anthracycline and dual HER2-targeted mAbs than in those treated with anthracycline-free regimens, which is consistent with previous published reports.[1,8,9] In the TRAIN-2 (Neoadjuvant Chemotherapy in HER2 Positive Breast Cancer) trial that compared dual HER2-targeted mAbs with or without anthracycline-containing regimens, cancer-related outcomes were similar for patients treated with and without anthracyclines. At a median follow-up of 3 years, 7.7% of patients treated with anthracyclines developed HF (defined as a decline in LVEF of 10% or more and LVEF <50%), which was significantly more frequent than in those treated without anthracyclines (3.2%; $P = 0.04$).[9] Similarly, in the BERENICE (A Study Evaluating Pertuzumab [Perjeta] Combined With Trastuzumab [Herceptin] and Standard Anthracycline-based Chemotherapy in Participants With Human Epidermal Growth Factor Receptor 2 [HER2]-Positive Locally Advanced, Inflammatory, or Early-stage Breast Cancer) trial, which was a required postmarketing study by the U.S. Food and Drug Administration after the approval of pertuzumab, patients received neoadjuvant anthracycline and dual HER2-targeted mAb therapies; 3% to 6.5% of patients developed New York Heart Association functional class 3 to 4 events.[8] However, the use of anthracyclines in combination with HER2-targeted treatments has fallen out of favor because it is associated with a higher rate of HF than nonanthracycline regimens.

There are limitations inherent to pharmacovigilance databases. Data extraction, as is performed in clinical trials, cannot be undertaken when mining databases. For example, in this study, it is unclear whether the patients were symptomatic, how they were monitored (there is likely variability between 130 countries), and the criteria used to determine if they had an event or not. Moreover, it is not possible to review data retrospectively to clarify because VigiBase is deidentified. Without scrutiny, the results are based on the accuracy of the entered data and must be taken as such. In terms of the statistical analysis, the relative risk can be estimated but proportion data cannot. This impacts the implications of the results because we feel that caution needs to be exhibited in using these data to make echocardiographic follow-up guidelines given the limitations inherent to these databases.

Ewer and Herson[10] provided a comprehensive review of the use of sporadic report databases for characterizing postmarket cardiovascular toxicity. They suggested to link the report database to patients' electronic medical records; although this approach would help scrutinize the data, it would also bring other challenges, such as problems with patient confidentiality. The U.S. Food and Drug Administration has issued best practices in postmarketing safety surveillance for their staff.[11] They described the systematic approach the agency takes to collecting postmarketing data. This approach starts with a reporting safety signal followed by a comprehensive evaluation; an assessment of the causal association; and, finally, a review of regulatory actions that may be required.

As we expand our cancer-directed therapy armamentarium, there is a need to develop pragmatic and systematic guidelines for postmarketing monitoring in which the collected data quality can be scrutinized to learn more about cancer and toxicity outcomes from real-world data to continue to improve patient outcomes.

In conclusion, when incorporating research data into clinical practice, the source of the data needs to be considered. Balancing the utility of clinical trial and real-world data represents a considerable

dilemma. One provides very detailed information from an often very selected patient population, whereas the other allows for longer-term follow-up of a very diverse patient population with the limitations discussed previously. A significant knowledge gap persists. The oncologic community would welcome strong and reproducible data regarding the true extent of cardiotoxicity, but for the present, we believe that estimations based on widely varying entry criteria into databases where individual instances of events cannot be adjudicated result in uncertainties given the need to verify that the reported extent of cardiotoxicity has been accurately and definitively defined.

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REFERENCES

1. Waliany S, Caswell-Jin J, Riaz F, et al. Pharmacovigilance analysis of heart failure associated with anti-HER2 monotherapies and combination regimens for cancer. *J Am Coll Cardiol CardioOnc*. 2023;5(1):85–98.

2. World Health Organization. The importance of pharmacovigilance. https://apps.who.int/iris/handle/10665/42493

3. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf*. 2004;13(8):519–523.

4. Waller P, van Puijenbroek E, Egberts A, Evans S. The reporting odds ratio versus the proportional reporting ratio: 'deuce'. *Pharmacoepidemiol Drug Saf*. 2004;13(8):525–526.

5. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. *J Am Coll Cardiol*. 2022;79(17):e263–e421.

6. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med*. 2022;386(12):1143–1154.

7. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2012;23(suppl 7). vii155-vii66.

8. Swain SM, Ewer MS, Viale G, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BE6RENICE): a phase II, open-label, multicenter, multinational cardiac safety study. *Ann Oncol*. 2018;29(3):646–653.

9. van der Voort A, van Ramshorst MS, van Werkhoven ED, et al. Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual ERBB2 blockade in patients with ERBB2-positive breast cancer: a secondary analysis of the TRAIN-2 randomized, phase 3 trial. *JAMA Oncol*. 2021;7(7):978–984.

10. Ewer MS, Herson J. Cardiovascular adverse events in oncology trials: understanding and appreciating the differences between clinical trial data and real-world reports. *Cardiooncology*. 2022;8(1):13.

11. Best practices in Drug and Biological Product Postmarket Safery Survillance for FDA Staff, Food and Drug Administration. Best practices in drug and biological product postmarket safety surveillance for FDA staff 2019. https://www.fda.gov/media/130216/download

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