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Cardiotoxicity and Cardiac Monitoring Among Chemotherapy-Treated Breast Cancer Patients

Mariana L. Henry, BS,[a] Jiangong Niu, PhD,[a] Ning Zhang, MS,[a] Sharon H. Giordano, MD, MPH,[a,b] Mariana Chavez-MacGregor, MD, MSc[a,b]

ABSTRACT

OBJECTIVES This study sought to determine the rate of chemotherapy-related cardiotoxicity and to estimate adherence to recommendations for cardiac monitoring among breast cancer patients treated with chemotherapy.

BACKGROUND Heart failure (HF) is a known complication associated with cancer therapies. Little is known regarding the rate of chemotherapy-related cardiotoxicity and adherence to recommendations for cardiac monitoring among chemotherapy-treated breast cancer patients.

METHODS Patients >18 years of age with a diagnosis of nonmetastatic invasive breast cancer between 2009 and 2014, treated with chemotherapy within 6 months of their diagnosis, were identified in the Truven Health MarketScan (IBM Watson Health, Cambridge, Massachusetts) database. HF, comorbidities, and treatment details were identified using diagnosis and billing codes. Analyses included descriptive statistics, Cox proportional hazard regression, and logistic regression.

RESULTS A total of 16,456 patients were included; the median age was 56 years old. Cardiotoxicity was identified in 4.2% of patients. Therapy with trastuzumab (hazard ratio [HR]: 2.01; 95% confidence interval [CI]: 1.72 to 2.36) and anthracyclines (HR: 1.53; 95% CI: 1.30 to 1.80), Deyo comorbidity scores (HR: 1.38; 95% CI: 1.15 to 1.66; HR: 2.47; 95% CI: 1.94 to 3.15 for scores of 1 and ≥2, respectively), hypertension (HR: 1.28, 95% CI: 1.09 to 1.51), and valve disease (HR: 1.93; 95% CI: 1.48 to 2.51) were associated with an increased risk of cardiotoxicity. Patients ≤35 years of age (HR: 0.37; 95% CI: 0.19 to 0.72) and 36 to 49 years of age (HR: 0.49; 95% CI: 0.38 to 0.62) were less likely to have cardiotoxicity than patients 65 years of age and older. Among 4,325 patients treated with trastuzumab, guideline-adherent cardiac monitoring was identified in 46.2% of patients. Therapies using anthracyclines (odds ratio [OR]: 1.58; 95% CI: 1.35 to 1.87), taxanes (OR: 1.63; 95% CI: 1.27 to 2.08), and radiation (OR: 1.22; 95% CI: 1.08 to 1.39) were associated with guideline-adherent monitoring.

CONCLUSIONS HF is an uncommon complication of breast cancer therapies. The risk was higher among patients treated with trastuzumab or anthracyclines and lower in younger patients. Cardiac monitoring among trastuzumab-treated patients should be a priority among high-risk patients and in the presence of comorbidities or other chemotherapies such as those using anthracyclines. (J Am Coll Cardiol Img 2018;11:1084–93)

From the [a]Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, Texas; and the [b]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas. Supported by National Cancer Institute Cancer Center grant 2P30 CA016672 to MD Anderson Cancer Center, and Cancer Prevention and Research Institute of Texas grant RP160674. Drs. Chavez-MacGregor and Giordano are supported by Susan G. Komen Breast Cancer Foundation grants SAC150061 and SAC110053. Dr. Chavez-MacGregor has served as a consultant for Pfizer and Roche. All other authors have reported that they have no industrial relationships relevant to the contents of this paper to disclose.

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After secondary malignancies, cardiovascular disease is the leading cause of morbidity and mortality among breast cancer survivors (1). These high rates are due in part to the cardiac toxicities of cancer therapies. Trastuzumab-based chemotherapy is the cornerstone of systemic therapy for patients with HER2-positive tumors (2). Trastuzumab is a monoclonal antibody with excellent tolerability, however, its use is associated with cardiotoxicity (2). Data from clinical trials suggest that trastuzumab cardiotoxicity rates range from 4.1% to 10% (3-6). Trastuzumab causes damage to the cardiac myocytes, which can lead to heart failure (HF) through a type II cardiotoxicity, characterized by its reversibility (2). Despite being reversible in patients who are recovering their cardiac function, to date, it is not possible to predict who will develop this complication; therefore, it is important to understand the incidence in the general population and identify at-risk patients.

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The National Comprehensive Cancer Network recommends cardiac monitoring before initiating trastuzumab treatment and every 3 months while taking the treatment (i.e., at 3, 6, 9, and 12 months) (7). Cardiac monitoring is usually performed with an echocardiogram or with radionuclide ventriculography (multiple-gated acquisition [MUGA] scans) (8). There is little information about patterns of cardiac monitoring in breast cancer patients. In a previous work we found that, among 2,203 breast cancer patients older than 65 years of age, 64% received suboptimal cardiac monitoring during trastuzumab therapy (8). Thavendiranathan et al. (9) found that, although the absolute risk of cancer treatment-related cardiotoxicity was lower in younger patients, the relative risks of cancer treatment-related cardiotoxicity in older patients were similar to those in younger patients, indicating the need for surveillance of cardiac dysfunction in this young population, which has been typically considered to be at low risk for such events. To the best of our knowledge, there are no data from insurance claims for either the rates or the factors associated with cardiotoxicity and guideline-adherent cardiac monitoring in young American patients. In the large cohort of breast cancer patients in the present study, we estimated the rate and determinants of cardiotoxicity associated with the use of chemotherapy and trastuzumab-based chemotherapy. In addition, we calculated the rate of cardiac monitoring among trastuzumab-treated patients and describe the pattern of cardiac monitoring according to age.

METHODS

DATA SOURCE AND DATA EXTRACTION. Female patients older than 18 years of age with nonmetastatic invasive breast cancer diagnosed between 2009 and 2014 were identified in the Truven Health MarketScan (IBM Watson Health, Cambridge, Massachusetts) database. This database includes de-identified patient-level health data from medical claims and prescription drug claims for insured employees, spouses, and their dependents throughout the United States. Data are from large employers, managed care organizations, hospitals, electronic medical record providers, and Medicare and Medicaid and are often used for health services research.

Patients were included if they had been treated with chemotherapy within the first 6 months after their diagnosis. Male breast cancer patients and patients with a history of HF or cancer were excluded from the study. Patients were followed from the date of their breast cancer diagnosis until they either died or lost insurance coverage. The last follow-up date was December 31, 2015.

DEFINITIONS. Cardiotoxicity was defined as an incident case of HF following a breast cancer diagnosis. HF after breast cancer diagnosis was identified using International Classification of Diseases version 9 (ICD-09) diagnosis codes 425, 428, and 785.51 in inpatient, facility, and outpatient claims, respectively. HF, therefore, denoted symptomatic and asymptomatic events, as data for symptoms were not available in the MarketScan database. Patients were noted as having HF if there was at least 1 claim in the inpatient file or at least 2 claims that were more than 30 days apart in the outpatient files.

Among patients treated with trastuzumab-based chemotherapy, we evaluated the rates of cardiac monitoring. Guideline-adherent cardiac monitoring was defined as a baseline cardiac evaluation performed within 4 months before the first dose of trastuzumab was administered and a subsequent follow-up cardiac evaluation performed at least every 4 months during trastuzumab therapy (8). Our group used this 4-month cutoff in previous work, and it was chosen to compensate for differences in scheduling, resources, or levels of accessibility to medical care (8). Baseline cardiac monitoring was defined as a test conducted before any trastuzumab dose. Follow-up cardiac monitoring was defined as monitoring every 4 months after initiating treatment. Methods for cardiac monitoring such as echocardiograms and MUGA scans were identified in the facility,

ABBREVATIONS AND ACRONYMS

HF = heart failure

MUGA = multiple-gated acquisition