Analysis of Influencing Factors of Cardiotoxicity in Breast Cancer Patients Receiving Targeted Therapy

Quynh T.N. Nguyen[1], Shwu-Jiuan Lin[1], Phung-Anh Nguyen[2], Thanh-Phuc Phan[3], Jason C. Hsu[2,3]

[1] PhD Program in School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan
[2] Clinical Data Center, Office of Data Science, Taipei Medical University, Taipei, Taiwan
[3] International PhD Program in Biotech and Healthcare Management, College of Management, Taipei Medical University, Taipei, Taiwan

OHDSI

TAIPEI MEDICAL UNIVERSITY

Background

Targeted therapies, which include monoclonal antibodies and kinase inhibitors (KIs), have been introduced to treat cancer for 20 years. Anti-HER2 therapies (trastuzumab, pertuzumab) and tyrosine kinase inhibitors (lapatinib, olaparib) have revolutionized breast cancer treatment in terms of improving survival.[1,2] Despite their critical role in cancer treatment, these therapies were also reported with many cardiac adverse events. Incidence rate of congestive heart failure for trastuzumab in a real-world study is 2.8%, which is higher than report from clinical trials.[3] A meta-analysis showed that trastuzumab increased risk of high-grade congestive heart failure in comparison with placebo.[4] Cardiotoxicity is also observed with other targeted therapies such as pertuzumab and lapatinib, although not as commonly as with trastuzumab.[5,6]

Cardiotoxicity may result in restricted indication of drug and impact patient's life quality. However, the use of targeted therapy is irreplaceable in breast cancer patients, particularly for patients with HER2-positive. A comprehensive understanding of factors affecting cardiotoxicity of targeted therapy is essential. In this study, we aimed to explore the influencing factors leading to targeted therapy-related cardiotoxicity and to provide recommendations for clinical practice based on the findings.

Methods

Data were collected from Taipei Medical University clinical research database (TMUCRD) which contains electronic medical records of 3 affiliated hospitals. All the datasets were mapped to the Observational Medical Outcome Partnership common data model. The database consists of pathology report, hospitalization details, patient self-payment items, drug prescription and some laboratory data. Between 2008 and 2020, breast cancer patients treated at TMU's three affiliated hospitals were identified. We excluded patients aged younger than 20 years old and not treated with any of the studied targeted therapy (trastuzumab, pertuzumab, lapatinib, ribociclib, palbociclib, olaparib and everolimus). We also excluded patients who have preexisting cardiac diseases. The primary endpoint is cardiac adverse events, which consist of ischemia/ myocardial infarction, QT prolongation/ arrythmia, conduction disorders, heart failure and coronary artery diseases. Covariates include demographic characteristics, cancer stage, tumor size, comorbidities and comedications. We applied logistic regression model to assess the association of each influencing factor with the outcome.

Results

A total of 288 patients were included in this study. For demographic characteristics, both univariate and multivariate analysis showed that smoking and drinking were associated with cardiotoxicity. Other risk factors, such as hypertension, hyperlipidemia, diabetes, renal disease, and cerebrovascular disease, were also verified. Patients who use chemotherapy, as consistent with previous studies,[7] had a higher risk of cardiotoxicity (OR = 2.95, 95% CI: 1.09-7.96, p-value = 0.033). Cardioprotective medications (statins, beta blockers, calcium channel blockers, angiotensin II receptor blockers) were associated with a decreased risk of CAEs while the use of aspirin increased the risk many times (OR = 15.61, 95% CI: 5.88-41.48, p-value < 0.001).

Results

	crude OR (95%CI)	crude P value	adj. OR (95%CI)	P(Wald's test)
Age†	1.03 (1.02,1.04)	< 0.001	1.02 (1.01,1.04)	0.003
BMI†	1.06 (1.03,1.09)	< 0.001	1.0048 (0.9677,1.0432)	0.805
Smoking: ref.=No				
Unknown	1.2 (0.73,1.98)	0.464	2.56 (0.53,12.45)	0.245
Yes	1.72 (1.17,2.53)	0.006	2.38 (1.42,3.98)	0.001
Drinking: ref.=No				
Unknown	1.11 (0.7,1.75)	0.668	0.16 (0.04,0.67)	0.012
Yes	4.77 (3.3,6.91)	< 0.001	3.56 (2.21,5.74)	< 0.001
Tumor size†	0.98 (0.98,0.99)	< 0.001	0.98 (0.97,1)	0.008
Cancer stage: ref.=0				
1	3.36 (1.7,6.65)	< 0.001	3.9 (1.8,8.46)	< 0.001
2	2.54 (1.33,4.87)	0.005	2.52 (1.19,5.31)	0.015
3	1.9 (0.9,4.02)	0.094	2.34 (0.91,6.05)	0.079
4	1.14 (0.53,2.44)	0.744	1.2 (0.45,3.17)	0.72
Unknown	2.42 (1.07,5.49)	0.034	3.49 (1.22,9.99)	0.02
Comorbidities				
Hypertension	3.78 (2.9,4.92)	< 0.001	4.62 (3.07,6.94)	< 0.001
Hyperlipidemia	1.71 (1.27,2.31)	< 0.001	0.45 (0.28,0.72)	< 0.001
Renal disease	3.18 (1.94,5.21)	< 0.001	3.26 (1.66,6.4)	< 0.001
Lung disease	1.21 (0.74,1.96)	0.446	0.39 (0.2,0.76)	0.006
Diabetes	1.82 (1.3,2.53)	< 0.001	1.28 (0.78,2.12)	0.333
Cerebrovascular disease	1.95 (1.34,2.85)	< 0.001	2.98 (1.55,5.7)	0.001
Liver disease	1.39 (0.9,2.14)	0.141	1.69 (0.99,2.88)	0.053
Comedications				
Surgery	0.7 (0.44,1.1)	0.121	0.37 (0.17,0.82)	0.014
Radiotherapy	0.9901 (0.7722,1.2694)	0.937	0.68 (0.49,0.95)	0.022
Chemotherapy	2.6 (1.06,6.37)	0.036	2.95 (1.09,7.96)	0.033
Metformin	0.87 (0.53,1.43)	0.589	0.89 (0.49,1.62)	0.7
Statins	0.41 (0.24,0.71)	0.001	0.41 (0.2,0.83)	0.013
Aspirin	12.17 (6.43,23.06)	< 0.001	15.61 (5.88,41.48)	< 0.001
Beta blockers	0.31 (0.11,0.84)	0.022	0.14 (0.05,0.45)	< 0.001
Calcium channel blockers	0.3 (0.11,0.81)	0.018	0.25 (0.07,0.9)	0.034
Angiotensin II receptor blockers	0.67 (0.36,1.24)	0.207	0.41 (0.19,0.88)	0.021
Benzodiazepines	0.84 (0.54,1.29)	0.421	0.42 (0.24,0.73)	0.002

† Continuous variable

Conclusions

Results from our study showed that beside the well-known cardiac risk factors, the use of aspirin may significantly increase risk of cardiotoxicity in breast cancer patients treated with targeted therapy. Along with heart function assessment, cardioprotective drugs during oncology treatment should be considered for this population, particularly those at increased cardiovascular risk.

References

1. Lamon DJ, Rian Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001 Mar 15;344(11):783-92.
2. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006 Dec 28;355(26):2733-43.
3. Lidbrink E, Chmielowska E, Otremba B, et al. A real-world study of cardiac events in > 3700 patients with HER2-positive early breast cancer treated with trastuzumab: final analysis of the OHERA study. Breast Cancer Res Treat. 2019;174(1):187-196.
4. Long H, Lin Y, Zhang J, Zhong W, Zheng R. Risk of congestive heart failure in early breast cancer patients undergoing adjuvant treatment with trastuzumab: a meta-analysis. Oncologist. 2016;21(5):547-554.
5. Swain SM, Ewer MS, Cortés J, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. Oncologist. 2013;18(3):257.
6. Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. Mayo Clin Proc. 2008;83(6):679-686.
7. Yu H, Qiu Y, Wang Z, et al. Anthracycline induced cardiac disorders in childhood acute lymphoblastic leukemia: a single-centre, retrospective, observational study. Front Pharmacol. 2021;12.

Contact: jasonhsu@tmu.edu.tw