Cardiomyopathy Associated With Targeted Therapy for Breast Cancer

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ABSTRACT

Background: Chemotherapeutic agents directed against human epidermal growth factor receptor 2 (HER-2) have significantly improved the prognosis of patients who are positive for this receptor. However, cardiomyopathy remains as a common adverse effect of using these agents.

Materials and Methods: Literature search was conducted via PubMed using the keywords of "Trastuzumab Cardiomyopathy," "Lapatinib Cardiomyopathy" and "Pertuzumab Cardiomyopathy," which provided 104 results. These articles were then screened for relevance to the targeted subject based on their title and abstracts. Case reports and articles that were not discussing any aspect of cardiomyopathy secondary to targeted therapy for breast cancer and articles not in English were eliminated. After elimination, a bibliography search among selected articles was done and a total of 46 articles were identified. The collected articles were then meticulously analyzed and summarized.

Results: The use of human epidermal growth factor receptor 2 (HER-2) receptor targeted chemotherapy in breast cancer is limited because of a higher incidence (19–22%) of cardiomyopathy. The incidence of cardiomyopathy is not dose dependent and in most cases it is reversible after discontinuation of the drug and treatment with heart failure medications. Severe adverse outcomes including death or permanent disability are rare.

Conclusion: HER-2 targeted chemotherapy for breast cancer has a higher incidence of associated reversible cardiomyopathy. Patients should be monitored by serial echocardiography starting at the beginning of the treatment and followed by every 3 months until the completion of chemotherapy. Co-ordination between oncologists and cardiologists is needed to develop evidence-based protocols to prevent, identify, monitor and treat trastuzumab-induced cardiomyopathy.

Key Indexing Terms: Cardiomyopathy; Trastuzumab; Lapatinib; Pertuzumab; Breast cancer. **[Am J Med Sci 2016; 351(2):194–199.]**

INTRODUCTION

Breast cancer is one of the leading causes of cancer related deaths worldwide. Breast cancer is a major public health burden in North America.[1,2] It is the second most common cancer in the United States[3,4] with lifetime incidence of 11% and overall mortality of 3%.[1,2] More than 230,000 new cases and 40,000 deaths from breast cancer are reported annually in the United States[1,2]

Newer targeted therapy for breast cancer treatment has revolutionized the management of breast cancer. Trastuzumab (Herceptin) is a monoclonal antibody against human epidermal growth factor receptor 2 (HER2).[5] Trastuzumab is effective at reducing both progression and recurrence of breast cancer.[6,7] It reduces breast cancer recurrence and mortality by 50% and 33%, respectively.[7,8] It improves outcomes, increases the number of responders to chemotherapy and prolongs life in women with surgically removed or metastatic HER-2 positive breast cancer. The M77001 Study Group showed that when compared to docetaxel alone, trastuzumab plus docetaxel increased the overall survival of patients with HER-2 positive breast cancer (median = 31.2 versus 22.7 months).[9] The Herceptin Adjuvant (HERA) trial found that Trastuzumab significantly extended 4-year disease-free survival when used for 1 year after standard chemotherapy compared to observation for 1 year after standard chemotherapy (78.6% versus 72.2%, hazard ratio = 0.76, $P < 0.0001$).[10]

Targeted therapy, particularly toward HER-2 Neu receptors is however associated with an increased risk of cardiomyopathy. The following review summarizes current knowledge on cardiomyopathy associated with targeted therapy in breast cancer with emphasis on surveillance and treatment of such cardiomyopathy.

METHODS

Literature search was conducted via PubMed using the keywords "Trastuzumab Cardiomyopathy," "Lapatinib Cardiomyopathy" and "Pertuzumab Cardiomyopathy". The search resulted in 104 articles from January

1990 to September 2014. These articles were then screened for relevance to the targeted subject based on their title and abstracts. Case reports and articles that did not have discussion on any aspect of cardiomyopathy secondary to targeted therapy for breast cancer and articles not in English were eliminated. After elimination, a manual bibliography search among selected articles was performed and a total of 46 articles were identified. The collected articles were then meticulously analyzed and summarized.

TRASTUZUMAB-INDUCED CARDIOMYOPATHY

Definition

The definition of cardiomyopathy in the setting of use of trastuzumab and other targeted therapies for breast cancer is variable. Common definitions include a 10% drop in left ventricular ejection fraction (LVEF) from a baseline of 50–55% or any drop of less than 40% from baseline LVEF, with or without accompanying signs or symptoms of congestive heart failure (CHF). As part of the clinical trials for trastuzumab, Cardiac Review and Evaluation Committee defined cardiomyopathy as either a decline in global LVEF or a decrease in cardiac contractility that was more severe in the septum or signs or symptoms of CHF or a decline in LVEF of 5% to $<$55% with accompanying signs or symptoms of CHF or a decline in LVEF of at least 10% to $<$55% without accompanying signs or symptoms.[11]

Epidemiology

The incidence of cardiomyopathy reported in clinical trials varies widely and ranges from 7–27%.[11] Compared with clinical trials, the incidence of cardiomyopathy in patients on trastuzumab is significantly higher in community based observational studies with reported incidence from 20.5–33.1%.[12-14] In 2001, Slamon et al reported an 8.8–11% incidence of cardiomyopathy in patients receiving paclitaxel and Trastuzumab compared with only 1–4% in those who received paclitaxel alone. There was also a greater incidence of cardiotoxicity (26–28%) in patients receiving the combination of trastuzumab and anthracyline versus anthracycline alone (6–9.6%).[15] Seidman et al noted that the incidence of cardiomyopathy was the greatest in patients receiving concomitant trastuzumab and anthracylines plus cyclophosphamide (27%). The risk was lower in patients receiving paclitaxel and trastuzumab (13%) or trastuzumab alone (3–7%).[11] Bowles et al[16] reported that when compared with women who received no chemotherapy, there was a 4-fold increase in the risk of cardiomyopathy among women who received treatment with trastuzumab alone and a 7-fold increase in the risk of cardiomyopathy for those who received anthracyclines plus trastuzumab. Moreover, there also appears to be a higher incidence of cardiomyopathy in patients receiving trastuzumab for metastatic breast cancer when compared to those using trastuzumab as an adjuvant treatment.[17] This higher incidence of cardiomyopathy is of significant concern in metastatic breast cancer as 5-year survival with regional lymph node involvement is 77% whereas 5-year survival in heart failure is only 50%.[18] To date, however, adverse outcomes, including death or permanent disability because of trastuzumab-induced cardiomyopathy and heart failure are uncommon.

Risk of Cardiomyopathy With Trastuzumab

Common factors that increase the risk of cardiomyopathy with trastuzumab include age more than 50 years, preexisting cardiomyopathy, high body mass index, hypertension and concomitant use of anthracyclines and cyclophosphamide.[19] Age is a significant risk factor and a study documented an almost 2-fold increase in the risk of cardiomyopathy associated with trastuzumab in the elderly.[20] Also, African-Americans had an elevated risk of trastuzumab related cardiomyopathy.[21] There is a higher incidence of cardiomyopathy when trastuzumab is used in patients with metastatic breast cancer as compared with patients in whom trastuzumab was used as an adjuvant therapy as mentioned earlier.[17] Frequently considered risk factors including low baseline LVEF, history of radiation therapy to left chest or mediastinum, history of cardiac transplantation and a history of exposure to anthracyclines did not change the risk of cardiomyopathy from trastuzumab.[22]

Pathophysiology of Trastuzumab-Induced Cardiomyopathy

Animal studies, particularly in mice have shown that the absence of nitric oxide synthase 3 is associated with less severe cardiac dysfunction when exposed to trastuzumab in combination with doxorubicin (a drop in LVEF from 75–46% when compared to a drop in LVEF of 72–35%).[23] This was attributed to reduced free radical production in the mice that had mutated nitric oxide synthase enzyme. Trastuzumab may also cause ErbB2 mediated down regulation of BCL-XL and increased expression of BCL-XS and decreased adenosine triphosphate thereby causing apoptosis.[24] Lapatinib which also affects the ErbB2 receptor has lesser cardiac adverse effects[25] which lead some investigators to speculate the possibility of an antibody that may be generated by trastuzumab, which is not the case in Lapatinib (explaining its likely favorable cardiac adverse effect profile). Defects of innate immunity, particularly in toll like receptor 4 deficiency, reduced the chances of cardiomyopathy with trastuzumab.[26] A fascinating study showed that patients with New York Heart Association class III heart failure had higher levels of HER2 than controls implicating a possible role for ErbB2 in heart failure even in the absence of trastuzumab.[27]

Course of Trastuzumab-Induced Cardiomyopathy

Cardiomyopathy in the setting of trastuzumab use is not dose-dependent and mostly reversible. The incidence