Cardiac Side Effects of Targeted Therapies

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Objectives: *To review common cardiac side effects, their clinical presentation, and recommendations for assessment and management of patients receiving molecularly targeted cancer therapies.*

Data sources: *Peer-reviewed literature.*

Conclusion: *Although there is no established guideline for pretreatment cardiac evaluation and monitoring of patients receiving molecularly targeted agents, data currently supports the need for early risk identification and prevention/reduction strategies.*

Implications for Nursing Practice: *As nurses, we have a unique opportunity to help improve and maintain the quality of life of cancer survivors. Cardiovascular assessment and prevention/reduction strategies are essential to reduce risk of cardiovascular disease, promote optimal quality of life, and improve survival outcomes in patients receiving molecularly targeted cancer treatment.*

Key Words: *Cardiotoxicity, targeted therapy, cardiovascular assessment*

In recent decades, cancer research has led to a greater understanding of the pathophysiologic mechanisms involved in the development of cancer and subsequent introduction of molecular targeted cancer therapy (MTCT).[1] MTCT aims to interfere with specific biochemical pathways that are essential for development and growth of cancer cells. This new way of treating cancer has proven to be effective in several hematologic and solid tumors, with newer agents under development.[2-7]

These agents interfere with pathways that either promote cell survival or growth, or augment pathways that promote cell differentiation.[8] These pathways affect not only cancer cells but also normal cells, presenting the risk of adverse effects that may be longstanding. MTCT specifically has the potential to adversely impact cardiac and vascular function at the cardiomyocyte and endothelial cell level. As a result, cardiotoxicities such as left ventricular dysfunction, congestive heart failure, arrhythmias associated with QT prolongation or conduction disturbances, acute coronary syndrome, hypertension, and thromboembolism can occur[9,10] (see Table 1).[8,11-16]

Cardiovascular disease (CVD) is a competing cause of death in cancer survivors. Factors that influence cardiovascular risk (CVR) include years

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TABLE 1.
Cardiovascular Class Effects of Molecular Targeted Cancer Therapy

Molecular Targeted Therapy	Drug Examples	Categories	Cardiovascular Effects
HER2 inhibitors	Trastuzumab (Herceptin)	Monoclonal antibody	LV dysfunction, heart failure
	Pertuzumab (Projeta)	Monoclonal antibody	Unknown toxicity
	Lapatinib (Tykerb)	TKI	QT prolongation, heart failure
ABL-target inhibitors	Imatinib (Gleevec)	TKI	Hypertension, heart failure
	Dasatinib (Sprycel)	TKI	QT prolongation
	Nilotinib (Tasigna)	TKI	Hypertension, heart failure, QT prolongation, PVD
VEGF-RAS	Sunitinib (Sutent)	TKI	Hypertension, heart failure
	Sorafenib (Nexavaz)	TKI	Hypertension, heart failure
	Bevacizumab (Avastin)	Anti-VEGF	Hypertension, heart failure
Hormones-SERM	Tamoxifen (Nolvadex)	Mixed estrogen +anti estrogen activity	Lower total cholesterol, lower LDL, stroke, thromboembolism
	Toremifene (Farestin)	Mixed estrogen + anti estrogen activity	Lower total cholesterol, lower LDL, stroke, thromboembolism
	Anastrozole (Arimidex)	Aromatase inhibitor	Higher total cholesterol
	Letrozole (Femara)	Aromatase inhibitor	Higher total cholesterol
	Exemestane (Aromasin)	Aromatase inhibitor	Lower triglycerides, lower total cholesterol, lower LDL

Abbreviations: LV, left ventricular; LDL, low density lipoprotein; TKI, tyrosine kinase inhibitor; PVD, peripheral vascular disease; SERM, selective estrogen receptor modulation; VEGF, vascular endothelial growth factor.
Data from references 8, 11-15.
Herceptin, Genentech, South San Francisco, CA; Projeta, AbbVie, North Chicago, IL; Tykerb, Glaxosmithkline, Philadelphia, PA; Gleevec, Novartis, East Hanover, NJ; Sprycel, Bristol-Myers Squibb, Princeton, NJ; Tasigna, Novartis; Sutent, Pfizer, Groton, CT; Nekavar, Bayer Healthcare Pharmaceuticals, Whippany, NJ; Avastin, Genentech; Nolvadex, Astra Zeneca, Wilmington, DE; Fareston, GTx, Memphis, TN; Arimidex, Astra Zeneca; Femara, Novartis; Aromasin, Pfizer.

of cancer survival, age, pre-existing co-morbidities, and past treatment of primary, secondary, or metastatic disease.[8] A history of any of these factors places the patient receiving MTCT at greater risk for cardiotoxicity. This article will review the cardiovascular effects of MTCT (HER2 inhibitors, ABL-targeted inhibitors, anti-vascular endothelial growth factors, and hormones), discuss the complexity of CVD risk factors and their association with physiologic pathways of MTCT, the significance of CVD in mid-life and older adults, and provide screening and surveillance recommendations for CVR factors in patients with cancer.

Common Side Effects and Monitoring

Cardiotoxicity of HER2 Inhibitors: Trastuzumab, Pertuzumab and Lapatinib

The cardiac physiologic response to this category of drugs is related to the disruption in erbB-mediated cell protection/survival through changes in cellular metabolism, cytoskeleton structure, and the ability of the cardiac unit, the myocyte, to functionally respond to an electrical stimulus (known as excitation/coupling) important in maintaining normal sinus rhythm and function. Both the myocyte and cardiac endothelium express erbB receptors. Unlike the myocyte response to anthracyclines, Type 1 cardiotoxicity-irreversible myocyte death, the myocyte response to ErB2 inhibitors is reversible and is therefore classified as a Type 2 cardiotoxicity. The rate of left ventricular dysfunction associated with this class of drugs has been reported as 0.5% to 19% in past trials with trastuzumab.[11-13]

Lapatinib is a tyrosine kinase inhibitor (TKI) that targets both HER2-driven pathways and epidermal growth factor receptors. A neoadjuvant trial with dual HER2 inhibition consisting of trastuzumab and lapatinib increased the pathologic response of the cancer without any irreversible cardiac events.[14]

Like trastuzumab, pertuzumab is a monoclonal antibody that blocks the HER2 receptor. Cardiac outcomes in dual HER2 clinical trials combining pertuzumab and trastuzumab are yet to be determined, but data without increased risk of cardiotoxicity are promising.[15]