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Statement of Need

Scientific advances in the field of breast cancer have led to the diagnosis of cancer at earlier stages and the development of superior treatment strategies. These improvements have translated to better survival rates for patients with breast cancer and, as a result, the long-term side effects of breast cancer treatment have become an increasingly significant factor in patient outcomes. Chemotherapy has long been the cornerstone of adjuvant therapy for breast cancer, and cardiotoxicity is a notable side effect of several commonly-used chemotherapeutic agents, specifically anthracycline- and trastuzumab-based regimens. Although the long-term effects of cancer therapy have garnered more recent study, clear guidelines do not exist to help physicians detect and treat cardiotoxicity in patients with breast cancer. The purpose of this program is to increase participant awareness and understanding of chemotherapy-associated cardiotoxicity in breast cancer by helping physicians assess risk, implement appropriate diagnostic and monitoring strategies, and devise patient-specific treatment plans.

This activity is intended for cardiologists and oncologists.

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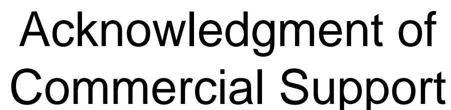

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Case Study: Monitoring & Managing Chemotherapy-Associated Cardiotoxicity in Breast Cancer

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Learning Objectives

- Recognize the importance of frequent cardiac monitoring and evaluate the use of periodic measurements of left ventricular ejection fraction as a means to monitor for chemotherapy-related cardiac dysfunction
- Assess evidence from trials examining the use of heart failure medications in the treatment of chemotherapy-induced cardiac dysfunction

Case Presentation

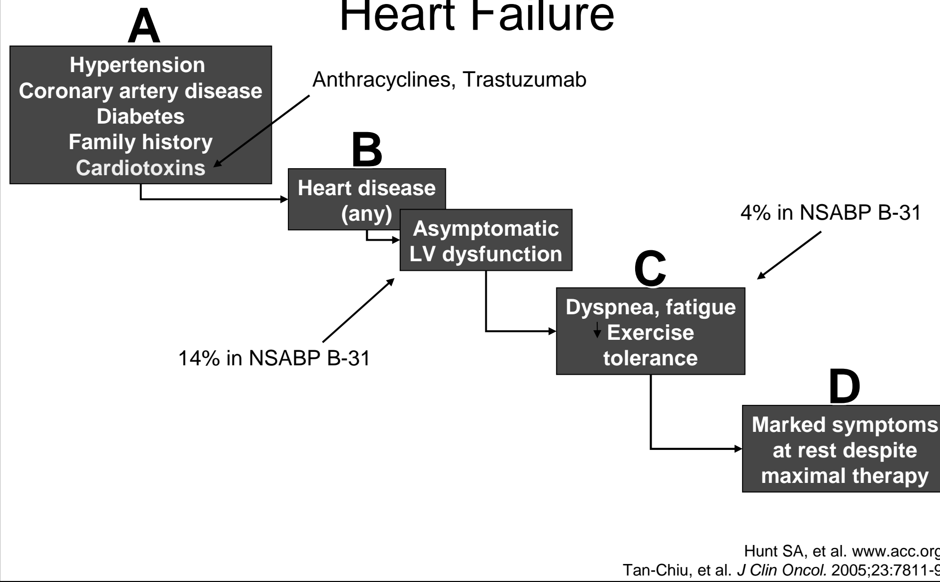
- HER2-positive breast cancer was diagnosed in a 54-year-old postmenopausal woman who exercises regularly and who is asymptomatic from a cardiac standpoint
- At age 24 years, following her second pregnancy, she experienced postpartum cardiomyopathy and was hospitalized for 6 weeks
  - Her ejection fraction at that time by M-mode echocardiography was 30%, she had an enlarged heart on x-ray, and her treatment included bed rest, digitalis, and diuretics
  - She recovered, stopped her medications some years later, and has not experienced cardiac problems or been followed up since

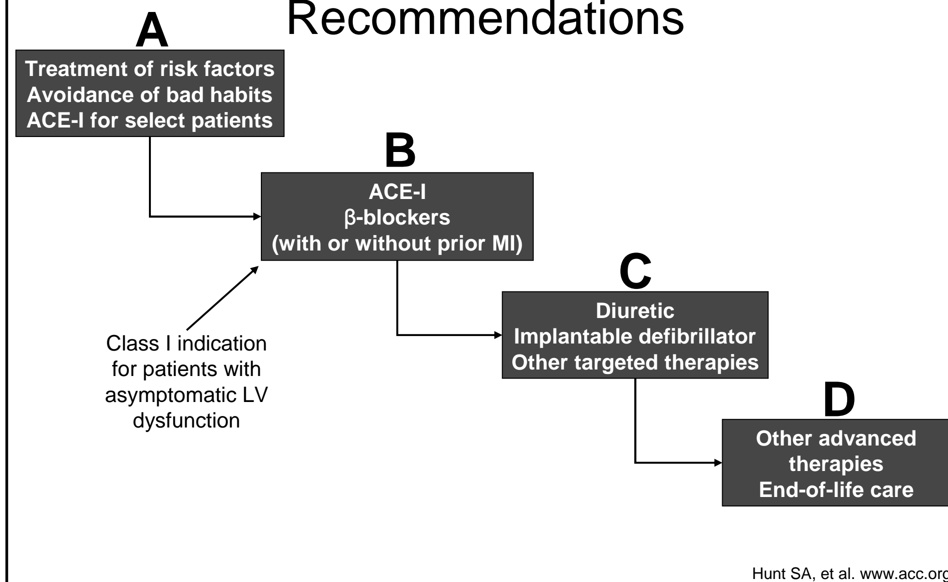
Case Presentation (cont.)

- At the time of the cardio-oncology consultation prior to treatment of her breast cancer:
  - She was asymptomatic and continued to exercise daily
  - Her cardiac examination results were normal
  - Her ejection fraction was 53% by 2-dimensional echocardiography, and she had normal left ventricular size
  - Her blood pressure was normal (128/78 mm Hg)
  - She took no medications
  - She had no history of diabetes, smoking, or other serious health problems

Case Presentation (cont.)

- The oncologist recommended an anthracycline-based regimen followed by trastuzumab x1 year with standard monitoring
  - What are the increased risks, if any, in this patient, and how should she be managed?


Clinical Stages in the Evolution of Heart Failure
A
Hypertension
Coronary artery disease
Diabetes
Family history
Cardiotoxins
Anthracyclines, Trastuzumab
B
Heart disease (any)
Asymptomatic LV dysfunction
14% in NSABP B-31
C
Dyspnea, fatigue
Exercise tolerance
4% in NSABP B-31
D
Marked symptoms at rest despite maximal therapy
Hunt SA, et al. www.acc.org.
Tan-Chiu, et al. J Clin Oncol. 2005;23:7811-9.


ACC/AHA Class I CHF Treatment Recommendations
A
Treatment of risk factors
Avoidance of bad habits
ACE-I for select patients
B
ACE-I
β-blockers
(with or without prior MI)
Class I indication for patients with asymptomatic LV dysfunction
C
Diuretic
Implantable defibrillator
Other targeted therapies
D
Other advanced therapies
End-of-life care
Hunt SA, et al. www.acc.org.

Reducing Cardiotoxicity and Managing Complications

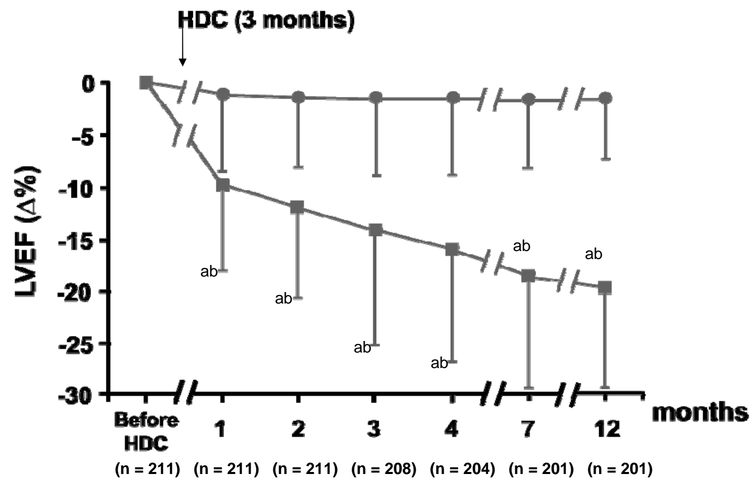
- Cease drug administration (?)
- Increase length of infusion (anthracyclines)
- Switch dosage form (anthracyclines)
  - Liposomal formulation may decrease toxicity
- Use fewer cardiotoxic agents in combination therapy
  - eg, docetaxel vs. paclitaxel
- Treat cardiac risk factors
- Treat LV dysfunction
  - ACEI and β-blocker use established in AIC
  - Is there a role for treatment in trastuzumab-associated cardiotoxicity?
  - WHEN should pharmacologic treatment be initiated?

Biomarkers for Early Detection of Cardiotoxicity

- Natriuretic peptides have been measured in small studies with mixed results
  - NT-ANP and BNP were raised during the first year after moderate-dose adjuvant epirubicin-based chemotherapy in 40 women treated for high-risk breast cancer[1]
  - An increase in plasma BNP was observed in 27 patients who received anthracycline chemotherapy[2]

1. Meinardi MT, et al. *J Clin Oncol.* 2001;19:2746-53.
2. Suzuki T, et al. *Am Heart J.* 1998;136:362-3.

Biomarkers for Early Detection of Cardiotoxicity



■ = TnI+ patients; ● = TnI- patients.

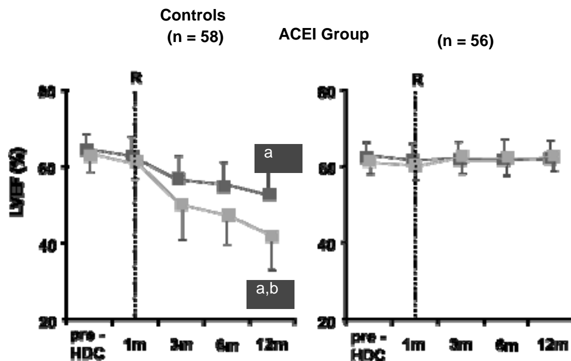
[a]$P < 0.001$ vs. before HDC. [b]$P < 0.01$ vs. TnI- group.

Cardinale D, et al. *Ann Oncol.* 2002;13:710-5.

Prediction *and* Prevention of HDC-Induced Cardiotoxicity?

Controls (n = 58)

ACEI Group (n = 56)



In high-risk, HDC-treated patients, defined by increased TnI, early treatment with enalapril 20 mg/day seemed to prevent the development of late cardiotoxicity

■ = patients without persistent TnI increase; ■ = patients with persistent TnI increase.

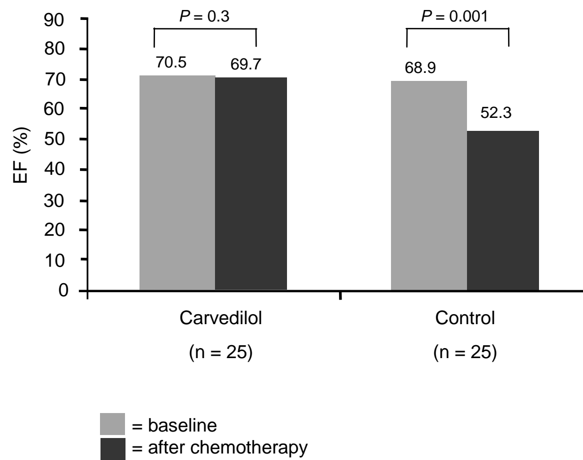
R, randomization; $P < 0.001$ for interaction between treatment and persistent TnI increase.

[a]$P < 0.001$ vs. baseline and randomization for all time points.

[b]$P < 0.001$ vs. patients without persistent TnI increase.

Cardinale D, et al. *Circulation.* 2006;114:2474-81.

Carvedilol Against Anthracycline-Induced Cardiomyopathy



Kalay N, et al. *J Am Coll Cardiol.* 2006;48:2258-62.

Guidelines for Monitoring Trastuzumab in NSABP B-31

Relationship of LVEF to LLN	Absolute Decrease in LVEF of < 10%	Absolute Decrease in LVEF of 10% to 15%	Absolute Decrease in LVEF of ≥ 16%
Within normal limits	Continue	Continue	Hold[a]
1%-5% below LLN	Continue	Hold[a]	Hold[a]
≥ 6% below LLN	Continue	Hold[a]	Hold[a]

[a]Repeat LVEF assessment after 4 weeks. If the criteria for continuation are met, resume trastuzumab treatment; if two consecutive holds or a total of three holds occurs, discontinue trastuzumab treatment.

Tan-Chiu E, et al. *J Clin Oncol.* 2005;23:7811-9.

Proposed Guidelines for Use of Adjuvant Trastuzumab Therapy

Physical Status	LVEF	Trastuzumab	LVEF Monitoring	Management
Asymptomatic	Normal	CONTINUE	As scheduled	None
	↓ < 16% but normal	CONTINUE	As scheduled	If LVEF < 40%, treat with an ACE inhibitor
	↓ ≥ 16% or subnormal (regardless of the amount of reduction)	HOLD TEMPORARILY	Repeat after 4 weeks; if improved, RESTART; if not improved, STOP	If LVEF < 40%, treat with an ACE inhibitor
Symptomatic	< Normal	HOLD PERMANENTLY	Per cardiologist's discretion	Treat for heart failure

Saad A, Abraham J. *Commun Oncol.* 2007;4:739-44.

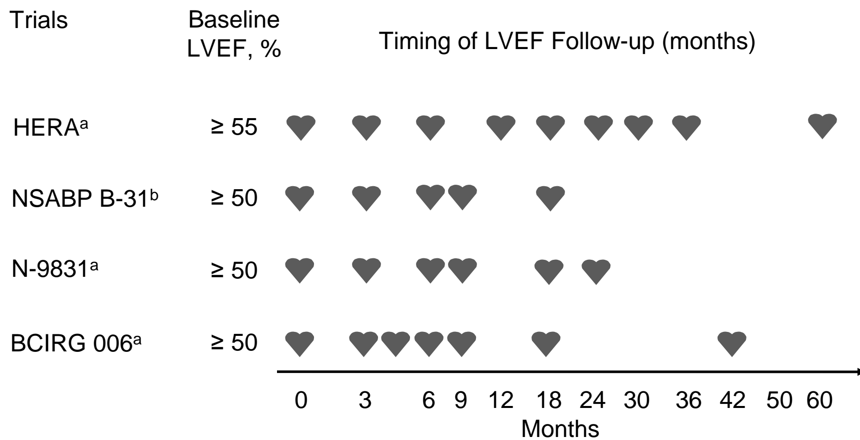
Proposed Guidelines for Trastuzumab Therapy in MBC

		Action		
Physical status[a]	LVEF	Trastuzumab	LVEF monitoring	Management
Asymptomatic	↓ but normal	CONTINUE	Repeat in 4 weeks	
	↓ > 10 points but normal	CONTINUE	Repeat in 4 weeks	Consider β-blockers
	↓ 10-20 points and LVEF > 40%	CONTINUE	Repeat in 2-4 weeks; if improved, MONITOR; if not improved, STOP	Treat for CHF
	↓ > 20 points to < 40% LVEF < 30%	HOLD	Repeat in 2 weeks; if improved to > 45%, RESTART; if not improved, STOP	Treat for CHF
Symptomatic	↓ < 10 points	CONTINUE		Search for noncardiac pathology (eg, anemia)
	↓ > 10 points and LVEF > 50%	CONTINUE	Repeat in 2-4 weeks; if stable or improved, CONTINUE; if worsened, STOP	Treat for CHF
	↓ < 30 points	STOP		Treat for CHF

[a]Heart rate and body weight should be monitored weekly. Asymptomatic is defined as changes in heart and or weight but without symptoms of dyspnea on exertion. Symptomatic is defined as a new, spontaneous (ie, unsolicited) report of symptoms of dyspnea on exertion, pulmonary vascular congestion, or edema.

Keefe DL. *Cancer.* 2002;95:1592-600.

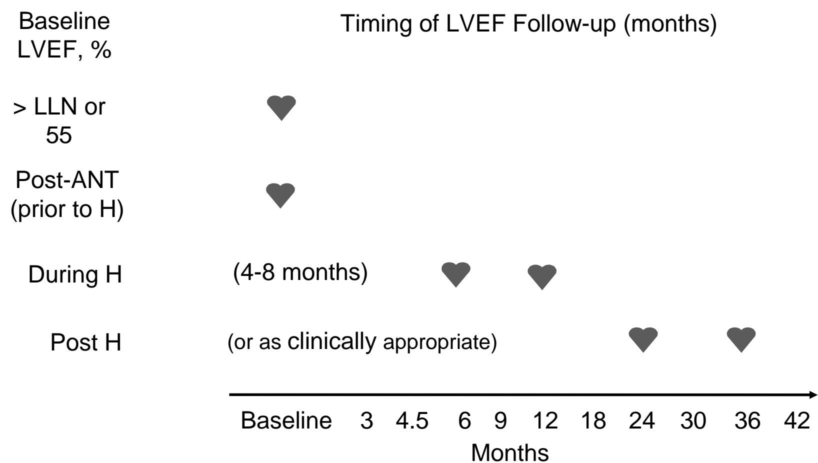
Baseline and Follow-up Cardiac Monitoring (as per adjuvant trials)



[a]MUGA or echocardiography.
[b]MUGA.

Piccart-Gebhart MJ, et al. *N Engl J Med.* 2005;353:1659-72.
Tan-Chiu, et al. *J Clin Oncol.* 2005;23:7811-9.
Perez EA, et al. *J Clin Oncol.* 2008;26:1231-8.
Slamon D, et al. BCIRG 006 Presentation. SABCS 2009. www.bcirg.org.

Baseline and Follow-up Cardiac Monitoring (our recommendations)



Appendix: Abbreviations and Acronyms

- ACEI = angiotensin-converting enzyme inhibitor
- AIC = anthracycline-induced cardiotoxicity
- ANT = anthracycline
- BNP = brain natriuretic peptide
- BCIRG 006 = The Breast Cancer International Research Group 006 trial
- CHF = congestive heart failure
- EF = ejection fraction
- H = trastuzumab
- HDC = high-dose chemotherapy
- HERA = The Herceptin Adjuvant trial
- HER2 = human epidermal growth factor receptor 2

Appendix: Abbreviations and Acronyms

- LLN = lower limit of normal
- LV = left ventricular
- LVEF = left ventricular ejection fraction
- MI = myocardial infarction
- MUGA = multiple-gated acquisition scan
- NCCTG N-9831 = The North Central Cancer Treatment Group N-9831 trial
- NSABP B-31 = The National Surgical Adjuvant Breast and Bowel Project B-31 trial
- NT-ANP = N-terminal atrial natriuretic peptide
- TnI = troponin I

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