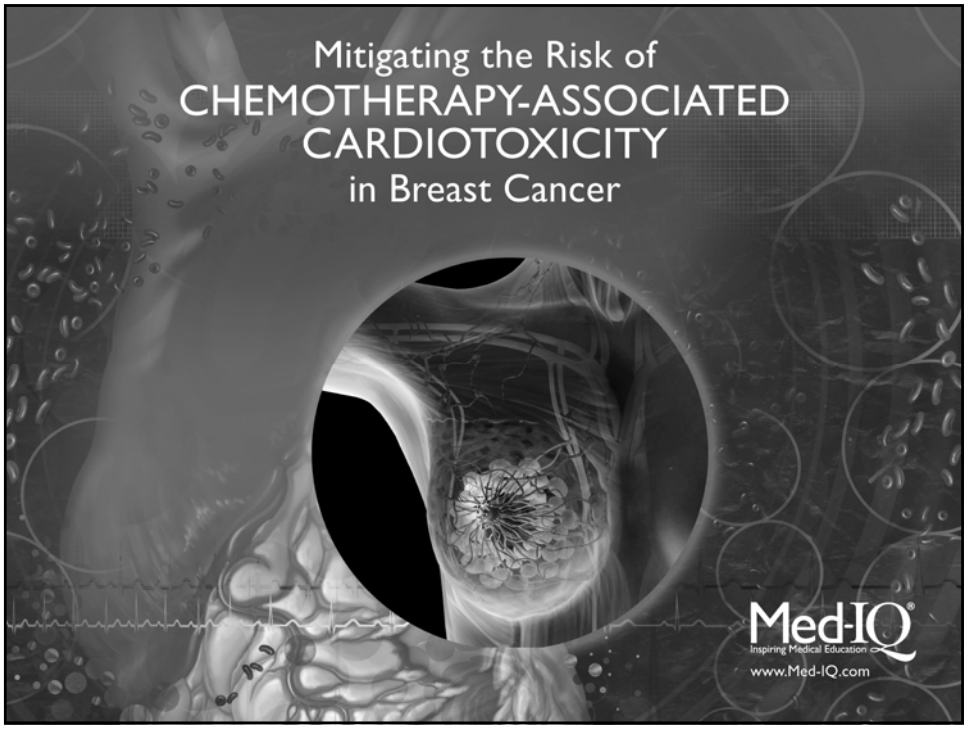

Statement of Need

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.

Target Audience

This activity is intended for cardiologists and oncologists.

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Michael S. Ewer, MD

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Mitigating the Risk of Chemotherapy-Associated Cardiotoxicity in Breast Cancer

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Learning Objectives

- Summarize available data on the risk of cardiotoxicity conferred by commonly used chemotherapeutic agents in the treatment of breast cancer
- Recognize patient risk factors associated with the development of cardiotoxicity in breast cancer patients
- Analyze the difference between Type I and Type II chemotherapy-related cardiotoxicity

Breast Cancer Patients Living Longer

- Breast cancer was diagnosed in an estimated 192,370 women in the US in 2009
- Advances have led to earlier diagnosis and better treatments, which have translated to better survival rates
- An estimated 2.5 million American women are living with or have a history of breast cancer
- Long-term toxicities of therapies take on greater significance

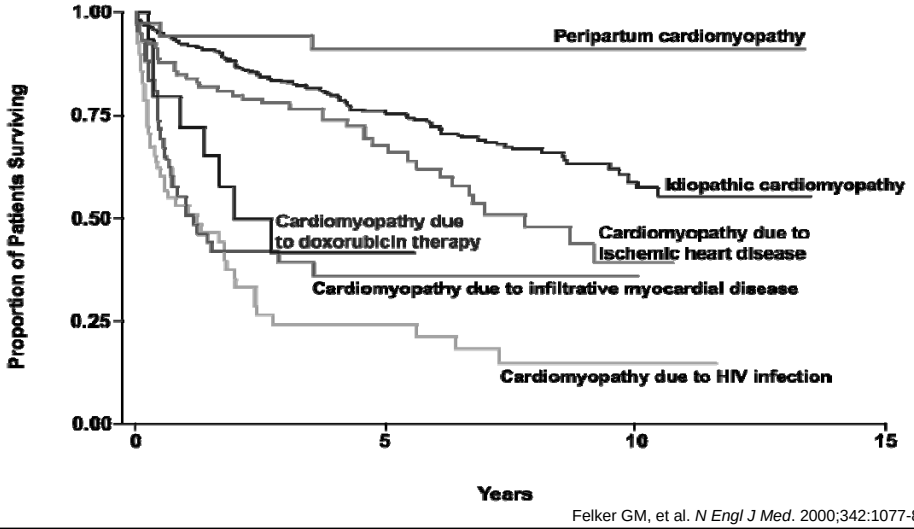
SEER Stat Fact Sheets – Cancer of the Breast. seer.cancer.gov/statfacts/html/breast.html.

Adverse Cardiovascular Effects of Cancer Therapies

Adverse Effect	Therapy
Heart failure	Anthracycline, mitomycin, cyclophosphamide, cisplatin, trastuzumab, alemtuzumab
Pericardial effusion	Cyclophosphamide, cytarabine, imatinib, busulfan, radiation therapy
Myocardial ischemia	Cisplatin, vinca alkaloids, capecitabine, IL-2, bevacizumab, 5-fluorouracil, radiation therapy
Arterial hypertension	Cisplatin, bevacizumab, interferon-α
Arterial hypotension	Etoposide, paclitaxel, alemtuzumab, cetuximab, rituximab, interleukin-2, interferon-α
Myocarditis	Busulfan, cyclophosphamide, radiation therapy
Bradycardia	Paclitaxel
Thromboembolus	Bevacizumab, paclitaxel

Galderisi M, et al. *Cardiovasc Ultrasound*. 2007;5:4.

Causes and Long-Term Survival in Initially Unexplained Cardiomyopathy



Felker GM, et al. *N Engl J Med*. 2000;342:1077-84.

Mechanisms of Cardiotoxicity

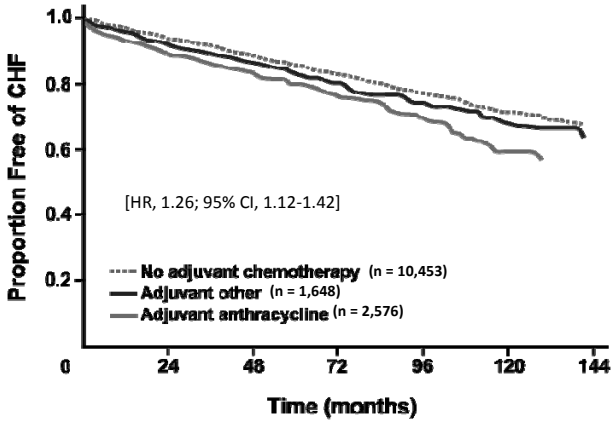
- Mechanisms of cardiac damage and clinical importance differ among therapeutic agents
- Single agents and combination therapies may contribute to cardiac damage independently or synergistically
- Subclinical damage can lead to later cardiac dysfunction or late sequential stress

Anthracyclines

- Cardiotoxicity is the major dose-limiting toxicity of anthracycline therapy
  - Decreased LVEF and congestive cardiomyopathy are the primary concerns
    - Can manifest early, late, or post-treatment, but early manifestation is uncommon because of compensation[1]
    - Risk relative to cumulative dose[2,3]
    - Can be treated, but once cells die, they are generally not replaced

1. Bristow MR, et al. *Am J Med*. 1978;65:823-32.
2. Von Hoff DD, et al. *Ann Intern Med*. 1979;91:710-7.
3. Swain SM, et al. *Cancer*. 2003;97:2869-79.

Incidence of CHF in Older Women on Adjuvant Anthracycline Therapy



Women aged 66-70 years: freedom from congestive heart failure (CHF) by adjuvant chemotherapy type

- Women aged 66-70 years treated with adjuvant anthracycline-based regimens were more likely to develop CHF
- Separation of the anthracycline-treated group from the non-anthracycline-treated groups increased with longer follow-up

Pinder MC, et al. *J Clin Oncol*. 2007;25:3808-15.

Trastuzumab

- Cardiac dysfunction and CHF incidence higher than expected[1]
  - Up to 4% incidence in adjuvant trials
  - Incidence greater with concomitant anthracycline chemotherapy[2]
  - Long-term implications less clear than those of anthracycline-induced cardiotoxicity[3]
- Asymptomatic declines in LVEF much more common[3]
- Cardiac damage manifests as late sequential stress when used following an anthracycline[4]

1. Slamon D, et al. *N Engl J Med*. 2001;344:783-92.
2. Seidman A, et al. *J Clin Oncol*. 2002;20:1215-21.
3. Sengupta P, et al. *Mayo Clin Proc*. 2008;83:197-203.
4. Ewer MS, et al. *Semin Oncol*. 1999;26:96-101.

Cardiotoxicity of Trastuzumab Plus Chemotherapy in Metastatic BC

	H + AC	AC	H + T[a]	T
Cardiac dysfunction[†] events, %	**27**	**8**	**13**	**1**
NYHA class III/IV CHF, %	**16**	**4**	**2**	**1**

[a]Almost all patients in this treatment arm had previous exposure to anthracyclines

[†]Criteria for Diagnosis of Cardiac Dysfunction

a) Cardiomyopathy characterized by a decrease in LVEF
b) Symptoms of CHF
c) Associated signs of CHF
d) Decline in LVEF of ≥ 5% to < 55% with signs/symptoms of CHF;
OR
e) Decline in LVEF of ≥ 10% to < 55% without signs/symptoms

AC = doxorubicin + cyclophosphamide;
H = trastuzumab; T = paclitaxel.

Seidman A, et al. *J Clin Oncol*. 2002;20:1215-21.

Cardiotoxicity in the Adjuvant Trastuzumab Trials

Clinical Trial	Cardiac Measure	Treatment Regimen	Incidence of Cardiac Events
NSABP B-31[1]	**NYHA III/IV CHF or cardiac death at 3 years**	**AC →T** **AC →T + H**	**0.8% (n = 814)** **4.1% (n = 850)**
NCCT N-9831[2]	**NYHA III/IV CHF or cardiac death at 3 years**	**AC →T** **AC →T →H** **AC →TH**	**0.3% (n = 664)** **2.8% (n = 710)** **3.3% (n = 570)**
HERA[3]	**Severe CHF**	**Observation** **H**	**0% (n = 1,719)** **0.8% (n = 1,682)**
BCIRG 006[4]	**Grade 3/4 CHF**	**AC →T** **AC→T + H** **TCH**	**0.3% (n = 1,050)** **1.96% (n = 1,068)** **0.4% (n = 1,056)**
FinHer[5]	**CHF/MI**	**D or V + FEC** **D or V + FEC →H**	**0% (n = 116)** **0% (n = 116)**

AC = doxorubicin + cyclophosphamide;
H = trastuzumab; T = paclitaxel; D = docetaxel; V = vinorelbine;
FEC = fluorouracil + epirubicin + cyclophosphamide.

1. Tan-Chiu E, et al. *J Clin Oncol.* 2005;23:7811-9.
2. Perez EA, et al. *J Clin Oncol*. 2008;26:1231-8.
3. St. Gallen Symposium 2009.
4. Slamon D. SABCS 2009.
5. Joensuu H, et al. *J Clin Oncol*. 2009;27:5685-92.

Type I and Type II Treatment-Related Toxicity

Type I (eg, Doxorubicin)	Type II (eg, Trastuzumab)
Myocyte death; permanent damage starts with first dose; bad prognosis[1]	Myocyte dysfunction; predominantly reversible; good prognosis[1]
Biopsy changes typical of anthracyclines[1]	No typical anthracycline-like biopsy changes[1]
Cumulative-dose related[1]	Not dose related[1]
Risk factors[2] Combination CT Prior or concomitant RT Age Previous cardiac disease Hypertension	Risk factors[2-4] Prior or concomitant anthracyclines Prior or concomitant paclitaxel Age Previous cardiac disease Obesity (BMI > 25 kg/m^2)

1. Ewer MS, Lippman SM. *J Clin Oncol*. 2005;23:2900-2.
2. Suter TM, et al. *Breast.* 2004;13:173-83.
3. Suter TM, et al. *J Clin Oncol.* 2007;25:3859-65.
4. Rastogi P, et al. ASCO 2007.

Cancer Therapy Cardiotoxicity: Risk Factors

Anthracyclines

- Cumulative dose
- Combination chemotherapy
- Prior or concomitant mediastinal radiotherapy
- Age (pediatric and elderly)
- Previous cardiac disease (associated with increased LVEDP)
- Hypertension

Trastuzumab

- Prior or concomitant anthracyclines
- Time on anthracyclines > anti-HER2
- Concomitant paclitaxel?
- Age > 50 years
- Previous cardiac disease (associated with systolic dysfunction; LVEF < 55%)
- Hypertension (medication)
- Higher BMI

Oxidative stress

Suter TM, et al. *Breast.* 2004;13:173-83.
Suter TM, et al. *J Clin Oncol.* 2007;25:3859-65.
Rastogi P, et al. ASCO 2007.
Jones RL, et al. *Expert Opin Drug Saf*. 2006;6:791-809.

Cardiotoxicity Risk Factors Simplified

- Anything that has already damaged the heart
- Anything that makes the heart more susceptible to ongoing stresses

End of story?

Cardiotoxicity Risk Factors: What Do We Need to Know?

- Why the risk factors are similar
- The impact of cardiac risk factors on cancer therapy-induced cardiotoxicity
- Many patients with cardiac risk factors are excluded from clinical trials
- No good studies have examined the risk factors for patients on trastuzumab who were not previously exposed to anthracyclines
- Oncologists and cardiologists need to work together to assess benefits vs. risks

Appendix: Abbreviations and Acronyms

- AC = doxorubicin + cyclophosphamide
- BC = breast cancer
- BCIRG 006 = The Breast Cancer International Research Group 006 trial
- BMI = body mass index
- CHF = congestive heart failure
- CI = confidence interval
- CT = chemotherapy
- Cum Inc = cumulative incidence
- D = docetaxel
- FEC = fluorouracil + epirubicin + cyclophosphamide
- FinHER = The Finnish HER2 trial
- H = trastuzumab

Appendix: Abbreviations and Acronyms

- HERA = The Herceptin Adjuvant trial
- HER2 = human epidermal growth factor receptor 2
- HR = hazard ratio
- LVEDP = left ventricular end diastolic pressure
- LVEF = left ventricular ejection fraction
- MI = myocardial infarction
- 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
- NYHA = New York Heart Association
- PTX = paclitaxel
- RT = radiation therapy

Appendix: Abbreviations and Acronyms

- T = paclitaxel
- TCH = docetaxel + carboplatin + trastuzumab
- V = vinorelbine

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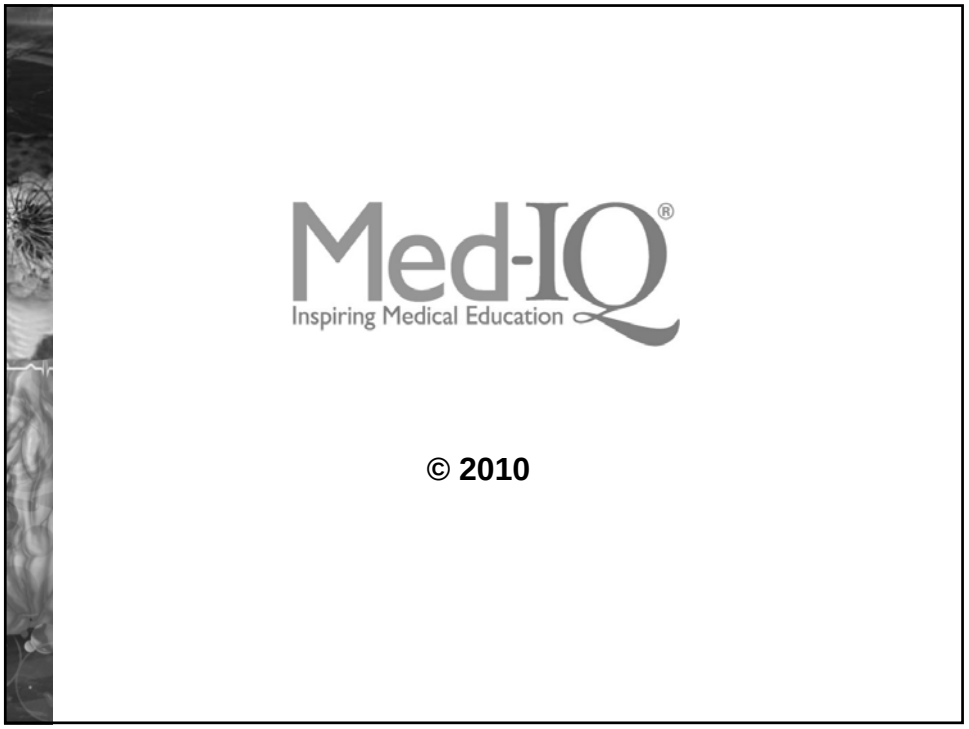
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