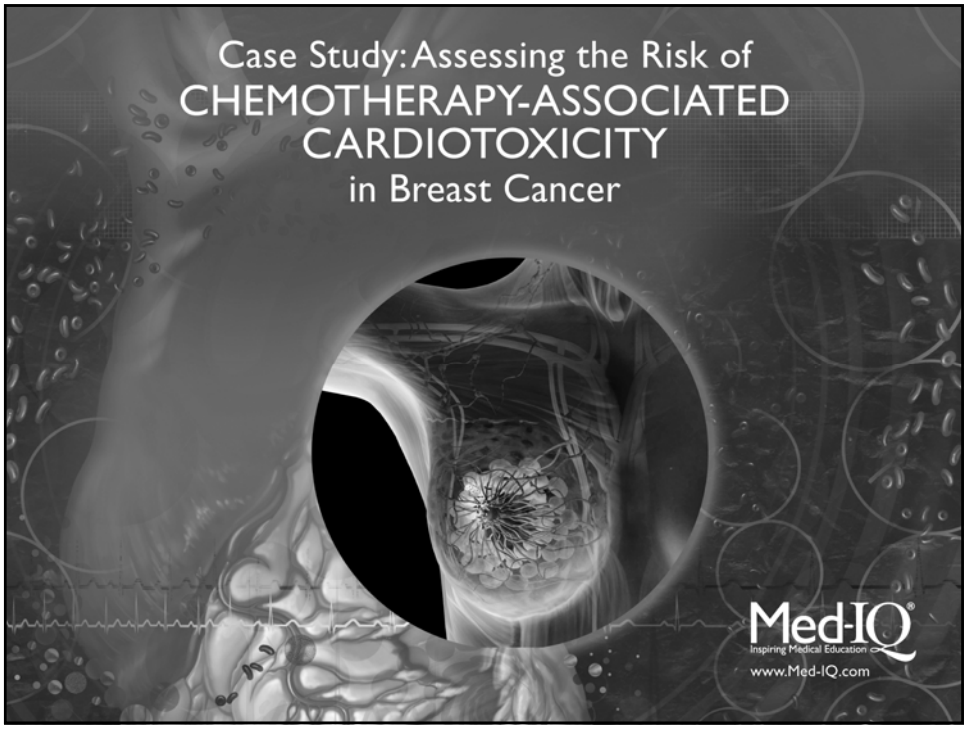

Statement of Need

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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William J. Gradishar, MD, has indicated no real or apparent conflicts.

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Case Study: Assessing the Risk of Chemotherapy-Associated Cardiotoxicity in Breast Cancer

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Learning Objectives

- Identify the risks and benefits of anthracycline therapy
- Outline recent clinical trials of alternative anthracycline preparations and non-anthracycline–containing regimens with a focus on side effect profiles and response rates

Case Presentation

- A 53-year-old postmenopausal African American woman presents following a screening mammogram demonstrating a 2-cm mass in the right breast; her ultrasound reveals a normal left breast and a 2-2.5–cm firm, but freely moveable, mass in the right breast at 3 o'clock; the right breast has no skin or nipple changes and no axillary nodes are palpable
- The patient undergoes a right breast biopsy, which demonstrated IDC, grade 3, ER/PR negative, and HER2 3+ (confirmatory FISH was positive)

Case Presentation (cont.)

- PMH: long-standing mild HTN controlled with diuretic, borderline obesity, no history of CHF or MI, and no family history of breast or ovarian cancer
- The patient undergoes a right lumpectomy and SLND, which reveals a 2.6-cm IDC and one positive SLD; complete axillary dissection reveals two additional positive axillary lymph nodes for a total of three positive axillary lymph nodes
- The patient presents for a discussion of adjuvant systemic therapy recommendations

Cardiotoxicity of 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 generally are 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.

Agents That Can Increase Anthracycline Cardiotoxicity

- Previous treatment with anthracyclines
- Paclitaxel[1]
  - May cause bradycardia, hypertension, or hypotension, and increases the plasma concentration of doxorubicin
- Trastuzumab[2]
  - Causes inherent but transient cardiac dysfunction
  - Interferes with cell-repair mechanisms, preventing potentially reversible anthracycline-damaged cells from recovery

1. Gianni L, et al. *Ann Oncol.* 2001;12:1067-73.
2. Ewer MS, et al. *Semin Oncol.* 1999;26:96-101.

Chemotherapy Alone vs. Chemotherapy + Trastuzumab

Endpoint	Chemotherapy Alone	Chemotherapy Plus Trastuzumab
Response rate*, % (% improvement)	**32**	**50 (53)**
Response duration*, months (% improvement)	**6.1**	**9.1 (58)**
Time to progression*, months (% improvement)	**4.6**	**7.4 (65)**
Median survival†, months	**20.3**	**25.1**

*$P < 0.0001$; †$P < 0.046$

Slamon D, et al. *N Engl J Med*. 2001;344:783-92.

Cardiac Outcomes With Trastuzumab in Combination With Chemotherapy

Cardiac Dysfunction Outcomes (CREC)	AC	H + AC	T	H + T[b]
Cardiac dysfunction events, n (%)[a]	9 (7)	39 (27)	2 (1)	11 (12)
Trastuzumab post-treatment events, n[a]	5	14	1	6
Deaths, n	1	4	2	1
MBC	0	4	2	0
Cardiac	1	0	0	0
Pneumonia	0	0	0	1

[a]*P* = 0.0001. [b]Almost all patients in this treatment arm had previous exposure to anthracyclines

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

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

Cardiotoxicity of Trastuzumab in Adjuvant Therapy

- Reports of cardiotoxicity from two trials of trastuzumab + paclitaxel following doxorubicin + cyclophosphamide:

Clinical Trial	Treatment Regimen	Incidence of Cardiac Events
NSABP B-31[1]	AC → T AC → T + H	0.8% 4.1%
BCIRG 006[2]	AC → T AC → T + H TCH	0.3% 1.96% 0.4%

- Single-arm trial of dose-dense AC (60/600 mg/m^2) followed by T + H (n = 70)[2]
  - 1 CHF at 4 months (LVEF ↓ from 75% to 45%)
  - 3 asymptomatic declines in LVEF at 6 months

AC = doxorubicin + cyclophosphamide;
H = trastuzumab; T = paclitaxel;
TCH = docetaxel + carboplatin + trastuzumab.

1. Tan-Chiu E, et al. J Clin Oncol. 2005;23:7811-9.
2. Slamon D. SABCS 2009.
3. Dang C, et al. *J Clin Oncol.* 2008;26:1216-22.

Ongoing Clinical Trials of Non-Anthracycline–Containing Regimens

- Two phase II, non-randomized efficacy studies address the issue of mitigating cardiotoxicity with non-anthracycline–based therapy
  - NCT00493649—"Adjuvant Docetaxel and Cyclophosphamide Plus Trastuzumab in Early Stage Breast Cancer Patients"[1]
  - NCT00542451—"Adjuvant Paclitaxel and Trastuzumab for Node-Negative HER2-Positive Breast Cancer"[2]

1. http://clinicaltrials.gov/ct2/show/NCT00493649.
2. http://clinicaltrials.gov/ct2/show/NCT00542451.

Analysis of Benefits vs. Risks

NSABP B-31 and NCCTG N-9831: Analysis of Benefits vs. Risks (at 3-year follow-up)

Survival Benefit of Trastuzumab at 3 Years[a]			Risk of Class III/IV CHF or Cardiac Death at 3 Years[b]			Risk of Asymptomatic or Symptomatic Cardiac Dysfunction[c]		
RR	ARR	NNT	RR	AR	NNT	RR	AR	NNH
0.67	**2.5%**	**40**	**5.1**	**4.1%**	**30.3**	**NA**	**18.9%**	**5.3**

AR = absolute risk; ARR = absolute risk reduction; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; RR = relative risk.
[a]From joint analysis of the NSABP B-31 and NCCTG N-9831 trials.
[b]From NSABP B-31 only.
[c]Requiring discontinuation of trastuzumab in the joint analysis.

Telli ML, et al. *J Clin Oncol*. 2007;25:3525-33.

Projected 10-Year Benefits vs. Risks

NSABP B-31 and NCCTG N-9831: Analysis of Projected Benefits vs. Risks

Projected 10-Year Survival After Chemotherapy	Projected 10-Year Survival Benefit of Trastuzumab			Projected 10-Year Cumulative Risk of Cardiotoxicity		
	AR (ACT)	AR (ACTH)[a]	NNT	AR (ACT)	AR (ACTH)	NNT
Low risk (80%)	20%	13.3%	15		Unknown	
Intermediate risk (60%)	40%	26.7%	7.5		Unknown	
High risk (40%)	60%	40%	5		Unknown	

ACT = doxorubicin, cyclophosphamide, paclitaxel; ACTH = ACT + trastuzumab;
AR = absolute risk; NNT = number needed to treat.
[a]Calculated using a relative risk of 0.67 assuming equal benefit in each risk category.

Telli ML, et al. *J Clin Oncol*. 2007;25:3525-33.

NSABP B-31
Cardiac Risk Score

- Factors associated with risk of developing a cardiac event:
  - Requirement for antihypertensive medications
  - Age ≥ 50 years
  - Post AC-LVEF values of 50% to 54%

Risk Score = $\frac{[7.4 + (0.03 \times \text{age}) - (0.1 \times \text{baseline LVEF}) + (0.68 \times C^a)] \times 100}{4.82}$

[a]C = HTN medication status: none = 0; yes = 1.

Rastogi P, et al. 2007 ASCO Meeting Proceedings. Abstract LBA513.
www.medscape.com/viewarticle/557942.

Risk/Benefit Summary

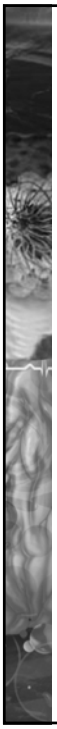
- Proven efficacy of trastuzumab when added to standard chemotherapy
- Trastuzumab-associated cardiotoxicity requires more study in the adjuvant setting, as it is being studied in non-anthracycline–containing regimens
- A multi-specialist approach is needed to implement strategies to reduce cardiotoxicity in breast cancer patients
  - Assess when and how toxicities manifest
  - Determine optimal combination therapies

Appendix: Abbreviations and Acronyms

- AC = doxorubicin + cyclophosphamide
- CHF = congestive heart failure
- CREC = Cardiac Review and Evaluation Committee
- ER/PR = estrogen receptor/progesterone receptor
- FISH = fluorescence in situ hybridization
- H = trastuzumab
- HER2 = human epidermal growth factor receptor 2
- HTN = hypertension
- IDC = invasive ductal carcinoma
- LVEF = left ventricular ejection fraction

Appendix:
Abbreviations and Acronyms

- MBC = metastatic breast cancer
- 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
- PMH = past medical history
- SLD = sentinel lymph node
- SLND = sentinel node biopsy
- T = paclitaxel
- TCH = docetaxel + carboplatin + trastuzumab



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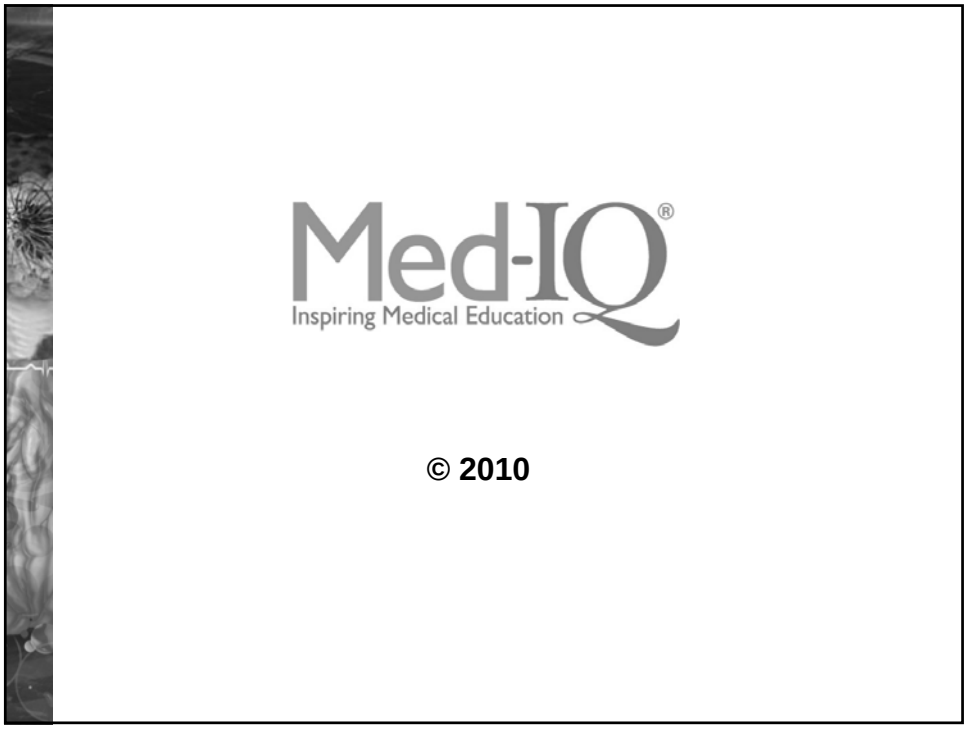
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