Modern Treatments for Breast Cancer: From Anthracyclines to CDK 4/6 Inhibitors

Roohi Ismail-Khan, MD, MS
Associate Member
Department of Breast Oncology
H. Lee Moffitt Cancer Center
Associate Professor
University of South Florida
Department of Oncological Sciences

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Heart disease and cancer are the first and second causes of death in women.
CANCER DEATH RATES FOR U.S. WOMEN, 1930-2005

Age-adjusted Death Rate per 100,000 Females

Year of Death


Lung and Bronchus
Breast
Colon and Rectum
Pancreas
Ovary
Uterus
Stomach
Clinical definitions of cardiotoxicity has been formulated by the cardiac review and evaluation committee which defined drug-associated cardiotoxicity as one or more of the following:

1. cardiomyopathy in terms of a reduction in left ventricular ejection fraction
2. symptoms associated with heart failure (HF)
3. signs associated with HF, such as S3 gallop, tachycardia, or both
4. reduction in LVEF from baseline
   • in the range of less than or equal to 5% to less than 55% with accompanying signs or symptoms of HF
   or
   • reduction in LVEF in the range of equal to or greater than 10% to less than 55%, without accompanying signs or symptoms

This definition does not include subclinical cardiovascular damage that may occur early in response to some chemotherapeutic agents.
Why do we need a Cardio-Oncology clinic from the Breast cancer perspective?

» Detection and treatment of breast cancer has significantly improved survival of breast cancer patients

» Side effects of adjuvant breast cancer therapy, including cardiotoxicity is clinically important and can increase morbidity/mortality

» New treatments/novel therapy pose an increased risk of cardiotoxicity in the metastatic setting

» As patients live longer, they develop cumulative cardiac risk factors
As a breast oncologist, what do I consider in an individual patient?

- We know that a single breast cancer patient may receive *multiple treatments* that affect cardiac risk, including anthracyclines, trastuzumab, taxanes and multiple new novel agents as well as radiation therapy, all of which can increase risk of cardiac disease.
- This risk is magnified in patients who carry a *genetic mutation* increasing their risk for *multiple cancers in their lifetime*.
- Individual patients present *with their own inherent risk* including obesity, DMII, hypertension, coronary artery disease, arrhythmias.
- These individual risks are cumulative in one individual patient.
- The treatment therefore must be individualized in a multidisciplinary model to fit each patient to decrease cardiac toxicity.
Moffitt’s Model: Patient Centred Care

- Takes into account patients’ needs and preferences
- Patients have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals
- Treatment is always MULTIDISCIPLINARY:
  - Surgery, medical oncology, radiation oncology, social work, nutrition, mental health, and Cardio Oncology
- One stop treatment of not only cancer
Back to the Basics
What is the baseline HF Risk in the General Population?

» According to American Heart Association data:
  > Range of risk between 0.3% (women under 30) and 11.8% (elderly)
  > Prevalence of heart failure for the general U.S. population (including males and females) over age 18 is estimated at 2%
Cardiac myocyte damage from doxorubicin has previously been attributed to the production of toxic reactive oxygen species (ROS) and an increase in oxidative stress.

Later studies implicate the topoisomerase-II (Top2) enzyme.

In cancer cells, anthracyclines target the enzyme Top2. In cardiac myocytes, the same process causes oxidative stress and DNA damage.

Other mechanisms proposed to contribute to anthracycline cardiotoxicity include mitochondrial iron accumulation and dysregulation of cardiomyocyte autophagy.
Use (and disuse) of Anthracyclines

» Breast Oncologists have decreased the use of anthracyclines as more data helps reassure breast oncologists that in certain populations, we may be able to avoid treatment with Anthracyclines

» (TC) Docetaxel plus Cyclophosphamide or Carboplatin plus Paclitaxel are often used instead of Adriamycin combinations in early breast cancers

» Unfortunately, many patients still require Anthracyclines as part of their treatment plan as oncologists still tend to lean towards including Anthracyclines in high risk and younger breast cancer patients
Age and cumulative dose

Cumulative risk of chronic heart failure (%) vs. Cumulative dose of doxorubicin (mg/m²)

- Age <15
- Age 40-59
- Age 15-39
- Age >60

Source: Ann Oncol © 2009 Oxford University Press
Impact of Trastuzumab?

1. Doubled response rates and PFS in HER 2 positive patients

2. Significantly increased cardiac toxicity
**Trials that made Trastuzumab SOC for HER2 positive breast cancer**

*adding them to anthracyclines*

**NSABP B-31**

» HER-2 +, node + breast cancer randomized to AC + T vs AC + T + 1 year of Herceptin

» 52% reduction in risk of recurrence and 33% reduction in risk of death

**HERA Trial (NEJM 2005)**

» 5,081 patients received 1-2 years of Herceptin following local therapy + standard chemo

» 1 year of adjuvant Herceptin reduced risk of a breast cancer recurrence by 46%
Types of Cardiac Dysfunction – proposed in 2005 in the JCO

- **Type I toxicity - Anthracyclines**
  - myocardial damage - irreversible
  - high likelihood of sequential stress related cardiac dysfunction

- **Type II toxicity - Trastuzumab**
  - was deemed to have a high likelihood of recovery to or near baseline cardiac status in 2-4 months with a low likelihood of sequential stress-related cardiac dysfunction
  - myocardial dysfunction - reversible
The Controversy

» study looked at 45,000 women age >66 with early-stage breast cancer and examined the incidence of HF based on cancer therapy received

» Data revealed that trastuzumab caused more long-term damage than anthracyclines in real-world patients with breast cancer

» the incidence of HF continued to increase with time, which went against the thought that trastuzumab-treated patients were not susceptible to sequential stress-induced cardiomyopathy in the same way that anthracycline-treated patients

» Surprisingly, **no real difference noted was noted in long term follow-up**
Is Trastuzumab toxicity really reversible?

Cumulative Incidence of HF (%)

Years After Diagnosis

- Anthra + Trastuz
- Anthra alone
- Trastuz alone
- Other chemo
- Other CA dx
Schedule of Cardiac Monitoring Via MUGA or Echo for Herceptin Therapy

- Baseline
- Chemo
- Every 3 months
- Herceptin
- Observation
- Every 6 months for $\geq 2$ years after completion of Herceptin in the adjuvant setting

MOFFITT CANCER CENTER

USF HEALTH
BCIRG 006: study to offer a non-anthracycline option

More patients* receiving TCH completed therapy compared to those receiving AC → TH

<table>
<thead>
<tr>
<th>Therapy</th>
<th>% of Patients Completing Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC → TH</td>
<td>73.5</td>
</tr>
<tr>
<td>TCH</td>
<td>86.3</td>
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</tbody>
</table>

Patients on the ACTH arm were not able to complete chemotherapy due to cardiac side effects.
**BCIRG 006: Incidence of Congestive Heart Failure**

Patients receiving TCH had lower rates of CHF

The incidence of NCI-CTC grade 3/4 cardiac ischemia/infarction was higher in the Herceptin-containing regimens: (AC → TH: 0.3% [3 of 1068] and TCH: 0.2% [2 of 1056]) as compared to none in AC → T
Adding Pertuzumab (increasing path CR rates)

» What about adding Pertuzumab?
» Will it increase cardiac risk?
» Tryphaena study tried to answer that question
» First adjuvant breast cancer study who primary end point was cardiac safety.
Neosphere - Treatment-naive women with HER2-positive breast cancer were randomly assigned to receive

- trastuzumab + docetaxel + pertuzumab
- trastuzumab plus docetaxel
- pertuzumab + trastuzumab
- pertuzumab + docetaxel

Patients given 3-drug regimen had a significantly improved pathological CR: **45.8%** vs trastuzumab + docetaxel (29%) or pertuzumab + trastuzumab (24%) or pertuzumab + docetaxel (16.8%)
What about cardiac toxicity? Tryphaena study

» **group A** 6 cycles FEC (concurrent 5-FU, Epirubicin, and Cyroxan plus trastuzumab plus pertuzumab)

» **group B** FEC sequential (5-FU, Epirubicin, and Cyroxan) x 3 followed by PTH x 3 trastuzumab plus pertuzumab plus docetaxel

» **group C** *(non anthracycline arm)* PTCH x 6 (trastuzumab plus pertuzumab plus docetaxel and carboplatin)

» *left ventricular systolic dysfunction*
  
  > Group A - 2/72 (2.8%),
  > Group B - 3/75 (4.0%) and
  > Group C - 4/76 (5.4%)

» **EF decline:** declines ≥10% from baseline to <50%.
  
  > Group A -8 (11.1%),
  > Group B - 12 (16.0%)
  > Group C - 9 (11.8%)
Phase II study that was conducted in 225 people HER2-positive, locally advanced, inflammatory, or early stage breast cancer with tumors greater than two centimeters.

The primary endpoint was cardiac safety

No new or unexpected cardiac AEs, or other AEs, were observed in any of the study arms.

At 5 years, f/u all arms were essentially equivalent when considering cardiac toxicity.
Treating endocrine therapy resistance in the new era

» MTOR inhibitors (Evrolimus)
» PI3K Inhibitors
» AKT Inhibitors
» CDK Inhibitors
  > Palbociclib
  > Abemaciclib
  > Ribociclib
CDK Inhibitors

» CDK 4/6 pathway has been found to be overactive in a number of cancers, including breast cancer.

» CDK 4/6 inhibition leads to activation of the tumor suppressor Rb, causing cell cycle arrest.

» Among postmenopausal women with hormone receptor-positive breast cancer, combinations of Aromatase Inhibitors with CDK 4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) have demonstrated significant improvement of PFS.
CDK inhibitors have tolerable side effects

- Side effects associated with all three drugs included leukopenia, fatigue, and nausea.
- Palbociclib and ribociclib cause neutropenia, although unlike the neutropenia that occurs with cytotoxic drugs, the neutropenia associated with CDK4/6 inhibitors is rapidly reversible.
- Abemaciclib has a greater selectivity for CDK4, therefore causes greater gastrointestinal–related toxicity and fatigue than plbociclib, but neutropenia is much better.
- Ribociclib is associated with QT prolongation but significantly less neutropenia or GU disturbances.
In three large studies, 1% of patients had a postbaseline QTcF value >500 ms, and 6% of patients had a >60 ms increase from baseline in QTcF interval.

- These changes were reversible with dose interruption.
- QTcF prolongation events tended to appear within the first 4 weeks of starting ribociclib.
Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 ms

Repeat ECG at approximately Day 14 of the first cycle and repeat at the beginning of the second cycle, and then as clinically indicated

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles

Correct any abnormality before starting KISQALI therapy

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation
• The observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen plus placebo subgroup compared with the AI plus placebo subgroup.

• In the placebo arm, an increase of >60 ms from baseline occurred in 6 of 90 patients (7%) receiving tamoxifen and in no patients receiving an NSAI.

• An increase of >60 ms from baseline in QTcF was observed in 14 of 87 patients (16%) receiving ribociclib plus tamoxifen and in 18 of 245 patients (7%) receiving ribociclib plus an NSAI.

• Ribo plus Tamoxifen was therefore not recommended.

• Ribociclib plus AI is a safe choice but EKGs must be monitored.
1. Does the presence of certain hereditary mutations affect risk of cardiac toxicity? We will hear about this tomorrow

2. Does risk stratification and cardiac rehabilitation improve outcome of patients undergoing systemic therapy with cardio-toxic agents? We will hear about this later today

3. Long term risk of cardio-toxic novel agents and effect on survival we will need to follow this over time
Impact of the BRCA mutation

Lifetime Risk of Breast Cancer

- General Population: 12%
- Familial (Family History without BRCA): 20%
- Hereditary (with BRCA Mutation): 87%
An exploratory study to determine if BRCA1 and BRCA2 mutation carriers have higher risk of cardiac toxicity


Published in Genes
Breast cancer type 1 and 2 susceptibility gene and protein product
» Human tumor suppressor genes
» Responsible for DNA repair by protecting cells against oxidative and genotoxic stressors
» Known malignancy risks
## Hypothesis provoking research

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<tr>
<th>Arm</th>
<th>Heart Failure</th>
<th>%</th>
<th>Total</th>
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<tbody>
<tr>
<td>BRCA1</td>
<td>15</td>
<td>6.6</td>
<td>227</td>
</tr>
<tr>
<td>BRCA2</td>
<td>10</td>
<td>6.1</td>
<td>164</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>6.4</td>
<td>391</td>
</tr>
<tr>
<td></td>
<td>Percent with Heart Failure</td>
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<tr>
<td><strong>BRCA-1</strong></td>
<td>6.61% <em>P</em> = &lt; 0.001</td>
<td>(95% CI: 3.75-10.66%)</td>
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<tr>
<td><strong>BRCA-2</strong></td>
<td>6.10% <em>P</em> = &lt; 0.001</td>
<td>(95% CI: 2.96-10.93%)</td>
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<tr>
<td><strong>Combined</strong></td>
<td>6.39% <em>P</em> = &lt; 0.001</td>
<td>(95% CI: 4.18-9.29%)</td>
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<tr>
<td><strong>General Population</strong></td>
<td>2.1%</td>
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</table>
Questions to answer

» The increased non-malignant mortality in BRCA patients *may* be due to heart failure and cardiotoxicity
» BRCA carriers may be at higher inherent risk of heart failure at baseline due to impaired double stranded DNA repair
» Arrhythmias may also play a role in cardiac toxicity and needs to be further evaluated
» Collaboration between cardiology and oncology is a must for the future of cancer survival
We understand the impact of breast cancer therapy and the importance of following our breast cancer survivors not only from a cancer perspective, but from a cardiovascular perspective.

We need to risk stratify and optimize patients who may have increased risk for cardiac toxicity.

Immunotherapy, novel drugs, combination therapy such as CDK inhibitors combined with MTOR inhibitor, other dual targeted therapy combinations, must be monitored during early phase clinical trials.
Through advocacy, research, and passion, we have come a long way in the treatment of breast cancer.

Now, we must assure that survival from one disease does not increase the risk of another disease.
Nadim Gaffar Khan, M.D.
Electrophysiologist
Suffered a TBI on 9/2/2016 at the hands of a drunk driver on the way to do a pacer here in FL. He continues to fight.

Please don’t drink and drive
If you do, please use uber/lyft
Please don’t text and drive
Drive safely

A special thank you to my favorite cardiologist