Comorbidity, Adherence and Breast Cancer Outcomes

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Aromatase Inhibitors and Breast Cancer Treatment

• Hormonal therapy is the most effective way to reduce recurrence in hormone sensitive breast cancers (EBCTG)
• AI’s standard of care for post menopausal women (ATAC)
• 10 years of therapy > 5 years (MA17r)
• AI + Ovarian Suppression > Tamoxifen for pre menopausal women (SOFT/TEXT)
• AI’s > Tam for DCIS (NSABP B35)
• AI’s effective for primary prevention (IBIS II)

Drugs don’t work in people who don’t take them!

C. Everett Koop, MD, US Surgeon General, 1985
Discontinuation and Non-adherence to BC hormonal therapy for women in Kaiser Permanente

Only 50% full duration >80%

Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer

Disease-free survival comparisons of patients who endocrine treatment according to the compliance score (BIG-198)
Why Are Treatments Not Started or Discontinued?

- COST
- Behavior
- Toxicity

Association Between Prescription Copayment Amount and Adherence

Change from Brand to Cheaper Generic Aromatase Inhibitors Increases Adherence
Household net worth, racial disparities and hormonal therapy adherence

Hershman DL et al, J Clin Oncol; 2015

Toxicity: Conceptual Framework

PATIENT FACTORS
- Cancer factors
- Symptom recognition
- Symptom management

TREATMENT

SYMPTOM

OUTCOME
- Survival
- QOL

ADHERENCE

PREVALENCE OF JOINT SYMPTOMS IN WOMEN ON AI’S FOR EARLY STAGE BC (N=200)

Prevalence of AI-Related Joint Symptoms

ADAC SAE = 8%
Cumulative incidence of stopping protocol-assigned endocrine treatment because of an adverse (BIG 1-98)

Chirgwin, P. et al, JCO 2016

PREDICTORS OF DISCONTINUATION: TOXICITY
Time to discontinuation

32.4% discontinued because of adverse effects
24.3% discontinued because of musculoskeletal symptoms

Hormone Discontinuation
The Breast Cancer Quality of Care Study (BQUAL)
Relationship Between Prior Medication Use and Endocrine Therapy Adherence

Comparison of adherence (MPR >80%) to non-cancer medications before and following breast cancer treatment

Yang, J; JOP 2016

P<0.01
Association Between Cardiovascular Risk Factors, Cardiac Events and Survival Outcomes Among Breast Cancer Patients Enrolled in SWOG Clinical Trials

- Cardiovascular is the primary cause of death among BC patients
- Various risk factors are common to the development of both BC and cardiovascular disease (e.g., diabetes and obesity)
- Patients with BC are at additional risk of developing incident cardiac conditions due to the cardiotoxic effects of various anticancer therapies such as radiation, anthracycline chemotherapies, and trastuzumab
- Secondary effects of treatment such as increased frailty and deconditioning can also contribute

We examined SWOG BC trials from 1999-2011.
- We identified baseline diabetes, hypertension, hypercholesterolemia, and coronary artery disease by linking trial records to Medicare claims.
- The primary outcome was overall survival.
- Patients with both baseline and follow-up claims were examined for cardiac events. Cox regression was used to assess the association between CVD-RFs and outcomes.

Cumulative incidence of cardiac events by statistically significant baseline cardiovascular disease risk factors
Survival by baseline cardiovascular comorbidity status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Survival</th>
<th>CVD Event-Free Survival</th>
<th>Cancer Event-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>1.22 (0.94-1.58)</td>
<td>1.32 (0.89-1.42)</td>
<td>1.23 (0.81-1.65)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>1.17 (0.88-1.56)</td>
<td>1.05 (0.82-1.33)</td>
<td>1.03 (0.75-1.41)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.73 (0.70-0.76)</td>
<td>0.80 (0.74-0.85)</td>
<td>0.79 (0.73-0.84)</td>
</tr>
<tr>
<td>CAD</td>
<td>1.10 (0.84-1.49)</td>
<td>1.12 (0.79-1.53)</td>
<td>1.10 (0.79-1.40)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.06 (0.71-1.55)</td>
<td>1.17 (0.80-1.66)</td>
<td>0.96 (0.62-1.49)</td>
</tr>
<tr>
<td>Number of baseline cardiovascular risk factors</td>
<td>2.51 (1.06-5.94)</td>
<td>3.12 (1.09-9.15)</td>
<td>1.15 (0.39-3.44)</td>
</tr>
<tr>
<td>Number of significant risk factors</td>
<td>1.13 (0.88-1.45)</td>
<td>1.27 (0.92-1.76)</td>
<td>1.16 (0.83-1.63)</td>
</tr>
</tbody>
</table>

Association Between Non-Adherence to Cardiovascular Medications Following Breast Cancer Diagnosis and Cardiovascular Events

- Using SEER-Medicare we identified women with Stage 1-3 breast cancer diagnosed 2008-2013 on oral medications for the treatment of hypertension, hyperlipidemia, and/or diabetes
- Subjects who were adherent prior to diagnosis were included.
- Adherence was defined as a medication possession ratio (MPR) of ≥80%.
- Adherence following BC was calculated between yrs. 1-2 after diagnosis
- Logistic regression: to define factors associated with non-adherence.
- Cox regression: to calculate the association between adherence and CVD events (ischemic event or heart failure) from 1 yr. after diagnosis
RESULTS

- 15,576 (67%) were adherent to >1 CVD med. at diagnosis.
- Among those adherent at baseline
  - 17.5% non-adherent to at least one medication
  - 19.2% were no longer adherent to antihypertensives
  - 26.2% were no longer adherent to cholesterol meds
  - 30.7% were not adherent to diabetes meds.
- Factors associated with non-adherence included:
  - Receipt of chemotherapy
  - Presence of comorbidities
  - Higher stage
  - Hormone receptor negative tumors.

Non-adherence to CVD meds following diagnosis was associated with an increased risk of having a cardiovascular event

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hazard ratio (95% Confidence Interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.33 (1.18 – 1.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.21 (1.05 – 1.40)</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.31 (1.10 – 1.56)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Cumulative Incidence of Cardiac Events Among those Adherent vs. Non-Adherent to CVD Medications

HYPERTENSION

CHOLESTEROL

DIABETES
The Association of Baseline Cardiovascular Risk Factors and Healthcare Utilization and Costs in Elderly Breast Cancer Patients

- We examined breast cancer patients treated uniformly on SWOG clinical trials from 1999-2011.
- We identified baseline diabetes, hypertension, hypercholesterolemia, and coronary artery disease (CAD) by linking trial records to Medicare claims; obesity was identified using clinical records.
- The outcomes were healthcare utilization (emergency room visits (ER), hospitalizations) and costs.
- Multivariable logistic and linear regression were used to assess the association between CVD-RFs and outcomes.

### Association of Number of CVD Risk Factors and Utilization

<table>
<thead>
<tr>
<th>Number of Utilizations</th>
<th>One Utilization</th>
<th>Two Utilizations</th>
<th>Three Utilizations</th>
<th>Four Utilizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>.08</td>
<td>&lt;.001</td>
<td>.009</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HTN</td>
<td>&lt;.001</td>
<td>.001</td>
<td>&lt;.001</td>
<td>.001</td>
</tr>
<tr>
<td>HCL</td>
<td>.001</td>
<td>&lt;.001</td>
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<td>&lt;.001</td>
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</tr>
<tr>
<td>Obesity</td>
<td>.001</td>
<td>&lt;.001</td>
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### Costs of Healthcare Utilization by Baseline Cardiovascular Risk Factors

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>HTN</th>
<th>HCL</th>
<th>CAD</th>
<th>Obesity</th>
<th>2 or more CVD-RFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>23.9%</td>
<td>57.7%</td>
<td>14.7%</td>
<td>71.1%</td>
<td>11.4%</td>
</tr>
<tr>
<td>ER</td>
<td>0%</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
<td>40%</td>
</tr>
</tbody>
</table>

### Table and CVD-Related Costs

- Diabetes: 23.9%
- HTN: 57.7%
- HCL: 14.7%
- CAD: 71.1%
- Obesity: 11.4%
- 2 or more CVD-RFs: 11.4%
Comorbidity and Clinical Trial Accrual

- The successful conduct of cancer clinical trials is made possible by the willing participation of patients.
- However, cancer patients rarely participate in trials, even though trials provide access to the newest treatments.
- Trial eligibility criteria exclude patients with many comorbid conditions out of concerns for safety as well as to establish a well-defined cohort of patients with a common clinical profile.
- We used data from a large, national web-based survey of cancer patients to examine the relationship between baseline disease health conditions, clinical-trial decision making and trial participation.

Comorbidity and Clinical Trial Accrual

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>None</th>
<th>&gt;1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio (95% CI)</td>
<td>( p = .02 )</td>
<td>( p = .02 )</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Trial Offer</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tr>
<th>Trial Offer</th>
<th>Odds ratio (95% CI)</th>
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<tbody>
<tr>
<td>Univariate</td>
<td>0.67 (0.58-0.78)</td>
</tr>
<tr>
<td>Multivariate</td>
<td>0.82 (0.70-0.96)</td>
</tr>
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<table>
<thead>
<tr>
<th>Trial Participation</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
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<tbody>
<tr>
<td>( p = .001 )</td>
<td>( p = .01 )</td>
<td></td>
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<th>Trial Participation</th>
<th>Odds ratio (95% CI)</th>
<th>( p = .001 )</th>
<th>( p = .01 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td>0.66 (0.55-0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate</td>
<td>0.76 (0.61-0.94)</td>
<td></td>
<td></td>
</tr>
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</table>
**Comorbidity and Clinical Trial Accrual**

- No Hepatic Restriction
- No Renal Restriction
- No CVD Restriction
- No Prior Malignancy Restriction
- No ASCO Category Restriction
- No Lung Restriction
- No Comorbidity Restriction

**Overall Participation Rate**
- Overall Rate: 9.02%, 9.1%, 9.37%, 9.39%, 9.68%, 9.27%, 10.26%

**Relative Increase**
- 0.01%, 0.88%, 3.87%, 4.15%, 7.28%, 2.75%, 13.82%

**New Trial Enrollments**
- 10, 767, 3361, 3602, 6318, 2384, 11992

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**Randomized Trial of a Medication Adherence Application to Improve Medication Adherence in Breast Cancer Survivors**

**Medication Reminder Applications**

- **RCT MED-APP** for pts with CVD disease for 3 months
  - Monthly Medication Adherence Scale (MMAS) compared with the usual care group (7.11 vs. 6.63, p=0.008), despite a higher than expected baseline adherence score in all groups.
  - The proportion in the low adherence group at 3-months was 18.8% in the App user group and 29.4% in the usual care group.
- **RCT HTN - MEDISAFE-BP**
  - Monthly Medication Adherence Scale (MMAS) compared with the usual care group (6.3 vs. 5.7, p=0.018)
- **HTN - IQVIA Cohort**
  - In a matched control cohort comparing patients using the Medsafe App to a matched control cohort of patients in IQVIA, patients using the app had a persistence rate of 81% at 12 months vs. 34% in the control group (p<0.001).
STUDY SCHEMA
Trial Goals

- this will be the first large-scale intervention trial to investigate a feasible, cost-effective strategy for improving global medication adherence.
- It is an intervention that involves the patient, provider and potentially the caregiver.
- We will be comprehensively measuring adherence by multiple modalities and will be assessing the association between adherence and cardiovascular endpoints.
- Apps are now widely available and inexpensive and therefore, if successful, it will be easily translatable into clinical use by insurance companies or other large-scale providers.

CONCLUSIONS

- A significant proportion of women are non-adherent to medications for chronic non-cancer conditions.
- Non-adherence to CVD medications was associated with an increased risk of a subsequent cardiac event.
- As breast cancer survival improves, physicians should pay particular attention to addressing CVD risk factors and medication adherence.
- Future studies will address adherence to hormone medications and medications for chronic conditions.