SYSTEMIC THERAPY OPTIONS FOR BREAST CANCER IN 2014

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1. Outline an approach to the systemic management of breast cancer patients
2. Review the importance of Hormone Receptor Status and HER2 status in the management of patients with breast cancer
3. Identify emerging trends in the systemic management of breast cancer.
Relationship with Commercial Interests/Support
- Consultant: patientordersets.com
- Honoraria: Lundbeck Oncology, AMGEN

Potential conflict(s) of interest:
- Not applicable.

Mitigation Potential Bias
- Not applicable
BREAST CANCER STATISTICS

- Breast Cancer is the most common cancer diagnosis in Women
  - 26% of all cancers diagnosed in women
- 2nd leading cause of cancer deaths
  - 14% of cancer deaths
- 5 year survival >80%

<table>
<thead>
<tr>
<th>Category</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Cases</td>
<td>200</td>
<td>23,800</td>
</tr>
<tr>
<td>Incidence Rate (per 100,000)</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>Deaths</td>
<td>60</td>
<td>5000</td>
</tr>
<tr>
<td>Death Rate (per 100,000)</td>
<td>0.3</td>
<td>19</td>
</tr>
<tr>
<td>5 y survival</td>
<td>80%</td>
<td>88%</td>
</tr>
</tbody>
</table>

One in 9 women is expected to be diagnosed with breast cancer in her life time.
BREAST CANCER STATISTICS

Age-Standardized Mortality Rates per 100,000
1983 - 2012 (estimated from 2008 to 2012)

Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2012
BREAST CANCER IS NOT ONE DISEASE
MANAGEMENT OF BREAST CANCER BY STAGE

Early Breast Cancer (%)
- Goal: Cure
- Surgery
- +/- Chemotherapy
- +/- Radiation
- +/- Hormonal Therapy

Locally Advanced Breast Cancer
- Goal: Surgical Resection, Cure
- Chemotherapy (hormonal)
- Surgery
- Radiation
- +/- Hormonal Therapy

Metastatic Breast Cancer
- Goal: Prolongation of life, palliation of symptoms
- +/- Hormonal therapy
- +/- Chemotherapy
- +/- Palliative Radiation
MANAGEMENT OF BREAST CANCER BY SUBTYPE

Sorlie et al. PNAS 2003
SURROGATES FOR MOLECULAR SUBTYPES OF BREAST CANCER

ER/PR
- 65-75%

HER2
- 15-20%

Triple Negative
- 15%

Luminal A
- High ER/PR expression
- Low grade

Luminal B
- Low ER/PR expression and/or HER2+
- HER2+

HER2+
- ER negative and HER2+
- High Grade

Basal Like
- ER/PR/HER2-
- CK5/6 + OR EGFR +

Normal

Claudin Low
- Metaplastic
- ER/PR/HER2-
HORMONE POSITIVE BREAST CANCER
OVERVIEW OF MANAGEMENT OF HORMONE POSITIVE BREAST CANCER

Figure: Conceptual Model of Luminal Breast Cancer Patterns in Relation to the Underlying Biology. CTx = chemotherapy; ER = estrogen receptor.
RISK STRATIFICATION FOR EARLY HORMONE POSITIVE BREAST CANCER

Traditional
- Lymph Node Status
- Size
- Grade
- Lymphovascular invasion
- ER/PR Status
- HER2 Status
- Age

Genomic
- OncotypeDx,
- Mammoprint
ONCOTYPEDx® FOR BREAST CANCER

**RESULTS**

Recurrence Score = 5

**CLINICAL EXPERIENCE: PROGNOSIS FOR NODE NEGATIVE, ER-POSITIVE PATIENTS**

The following results are from a clinical validation study of 1062 patients from the NSABP B-20 study. At 7 years median follow-up, 351 patients had a Recurrence Score of 5 and an average rate of distant recurrence of 5% (95% CI: 2.6-7.9%).

**HIGH RECURRENCE SCORE RESULT (≥31)**

- Large chemotherapy benefit
- 88% absolute benefit from Tam + chemo

**LOW RECURRENCE SCORE RESULT (<18)**

- Little to no chemotherapy benefit
- 97% 96% 91%

**INTERMEDIATE RECURRENCE SCORE RESULT (18–30)**

- No substantial chemotherapy benefit
- 189%
OVERVIEW OF MANAGEMENT OF EARLY HORMONE POSITIVE BREAST CANCER

- **Low Risk**: Hormonal Therapy
- **Intermediate Risk**: +/- Chemotherapy (TC) + Hormonal Therapy
- **High Risk**: Chemotherapy (FEC-D, AC/T, TC) + Hormonal Therapy
HORMONAL THERAPY FOR BREAST CANCER

Fulvestrant
• ER Antagonist
• Binds and degrades ER

BENEFIT OF TAMOXIFEN IN EARLY BREAST CANCER

Figure 8: About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality. 10,386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.
AROMATASE INHIBITORS – UP FRONT STRATEGY

ATAC – 10y F/U
(Lancet Oncology Dec 2010)
STRATEGIES FOR ADJUVANT HORMONES IN EARLY BREAST CANCER

- Tamoxifen Alone
- AI Alone
- Switch
- Extended
OVERVIEW OF MANAGEMENT OF HORMONE POSITIVE BREAST CANCER

Figure: Conceptual Model of Luminal Breast Cancer Patterns in Relation to the Underlying Biology. CTx = chemotherapy; ER = estrogen receptor.
## SIDE-EFFECTS COMPARISON

<table>
<thead>
<tr>
<th>Tamoxifen</th>
<th>AI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD</strong></td>
<td>√ (&lt;1% difference in serious CVD incidence)</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>√</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>√ slight</td>
</tr>
<tr>
<td><strong>VTE</strong></td>
<td>√</td>
</tr>
<tr>
<td><strong>Loss of BMD</strong>*</td>
<td>√</td>
</tr>
<tr>
<td><strong>Bone fracture</strong></td>
<td>√</td>
</tr>
<tr>
<td><strong>Osteoporosis</strong></td>
<td>√</td>
</tr>
<tr>
<td><strong>Musculoskeletal/arthralgia</strong></td>
<td>√</td>
</tr>
<tr>
<td><strong>Gynecologic AEs</strong></td>
<td>√ (uterine cancer, benign endometrial pathology, hysterectomy, vaginal discharge)</td>
</tr>
<tr>
<td><strong>Hot flashes</strong></td>
<td>√</td>
</tr>
</tbody>
</table>

Please note: √ represents higher risk of side-effect in column of that particular agent.

*BMD-bone mineral density*
Hormone positive breast cancer have an excellent long term prognosis.

Increasing use of genomic profiling of cancer has lead to better risk stratification of early hormone positive breast cancer and can lead to more appropriate treatment selection.

Treatment approached aimed at delaying late recurrences of increasing interest.

In metastatic setting new agents being introduced to overcome primary and secondary endocrine resistance.
HER2 POSITIVE BREAST CANCER
HER2 POSITIVE BREAST CANCER
HER2+ BREAST CANCERS HAVE THE MOST AGGRESSIVE PHENOTYPE

Clin Breast Can 2010
HERCEPTIN® (TRASTUZUMAB)
HERCEPTIN SIGNIFICANTLY ALTERED NATURAL HISTORY OF HER2 POSITIVE BREAST CANCERS
HERCEPTIN SIGNIFICANTLY ALTERED NATURAL HISTORY OF HER2 POSITIVE BREAST CANCERS

HER2/neu+ patients survival given Herceptin are similar to women with HER2/neu- cancers

\[ \text{Survival Free of Distant Recurrence} \] (% of patients)

\[ \text{Years} \]

\[ A: \text{HER2/neu+}, \text{trastuzumab} \]
\[ B: \text{HER2/neu-}, \text{no trastuzumab} \]
\[ C: \text{HER2/neu+}, \text{no trastuzumab} \]

\[ \text{ENGL J MED 354;8} \]
\[ WWW.NEJM.ORG \]
\[ FEBRUARY 23, 2006 \]
Mr. Connick gives Mr. Connick a tour of his lab at UCLA's Jonsson Comprehensive Cancer Center. "Going to Slamon's lab, I thought I would see something out of 'Star Trek,'" remarked Mr. Connick in an interview published in the New Orleans' Times-Picayune newspaper (June 22, 2008).
Pertuzumab and Trastuzumab

Complementary Mechanisms of Action

Trastuzumab:
- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Pertuzumab:
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

Baselga J, et al. [5]
PERTUZUMAB + TRASTUTUMAB + CHEMOTHERAPY

CLEOPATRA
Primary End Point

Progression-Free Survival, %

Ptz + T + D: median 18.5 mo
Pla + T + D: median 12.4 mo
Δ = 6.1 mo

HR = 0.62
95% CI 0.51-0.75
P < .0001

n at risk
Ptz + T + D 402 345 267 139 83 32 10 0 0
Pla + T + D 406 311 209 93 42 17 7 0 0

Baselga J, et al.[4,6]
Ado-Trastuzumab Emtansine (T-DM1) Structure

DM1 (derivative of maytansine)
MCC
Trastuzumab

Lo Russo PM, et al. [9]
TDMI (Kadcyla) in Advanced HER2+ Breast Cancer after Herceptin Failure

**Phase 3 EMILIA Trial**

**OS (Confirmatory Analysis)**

- **Median, mo**
  - Cap + Lap: 25.1, 182 events
  - T-DM1: 30.9, 149 events

- **Stratified HR = 0.682 (95% CI, 0.55, 0.85); P = .0006**
- **Efficacy stopping boundary P = .0037 or HR = 0.727**

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**Proportion Surviving**

- **Time, mo**
  - 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36

- **No. at risk:**
  - Cap + Lap: 496, 471, 453, 435, 403, 368, 297, 240, 204, 159, 133, 110, 86, 63, 45, 27, 17, 7, 4

**Data cut-off July 31, 2012; unstratified HR = 0.70; P = .0012.**

Verma S, et al. [16]
HER2 positive breast cancer remains one of the biggest successes of molecular targeted therapy in cancer.

Trastuzumab has significantly altered the natural history of HER2 positive breast cancer.

Multi-domain targeted anti-bodies and immuno-chemotherapy conjugates demonstrating exciting advances in survival.
TRIPLE NEGATIVE BREAST CANCERS
THE NEW "BAD ACTORS" OF BREAST CANCER

(A) Probability of survival vs. Relapse free survival
- Non-triple negative
- Triple negative

(B) Probability of survival vs. Overall survival
- Non-triple negative
- Triple negative

$p < 0.001$
$p = 0.021$

Keam BMC Cancer 2007
THE NEW “BAD ACTORS” OF BREAST CANCER

**Figure 2. Sites of First Distant Recurrence in Cases of Metastatic Triple-Negative Breast Cancer as Compared with Non-Triple-Negative Breast Cancer.**

The percentages shown are approximate percentages of women with a first distant recurrence among women in whom metastases develop. Data are from Dent et al., Rodriguez-Pinilla et al., and Liedtke et al.
THE NEW “BAD ACTORS” OF BREAST CANCER

Median Duration of Palliative Chemotherapy for TNBC

- First-Line: 11.9 Weeks
- Second-Line: 9 Weeks
- Third-Line: 4 Weeks

Overall Survival from Metastasis to Death for TNBC

- Median Overall Survival: 13.3 Months

Kassam Clin Breast Cancer 2009
Identifying TNBC

- Young Age
- Premenopausal
- Black Women
- BRCA1
- Early age of first child
- High Grade
- LABC
- Interval Cancers

10-30% Triple negative but not Basal
   Eg apocrine Claudin Low

15-40% Basal like but not Triple Negative
TRIPLE NEGATIVE BREAST CANCERS ARE CHEMO-RESPONSIVE

Liedtke J Clin Oncol 2008
Laporte Cancer Res 2009
TARGETED THERAPIES OF INCONSISTENT BENEFIT IN TRIPLE NEGATIVE BREAST CANCER

Platinum Chemotherapy

PARP Inhibition

Overall Survival - Metastatic Patients

- Triple Negative (n=34)
- Other (n=121)

\[ p = 0.1 \]
TRIPLE NEGATIVE BREAST CANCER

SUMMARY

- Remain an area of high need in breast cancer research
  - High risk of relapse
  - Poor survival in metastatic setting
- No identifiable target for drugs
- Likely represents a heterogeneous population of cancers
In 2014 numerous systemic therapy options available for breast cancer management.

Management of breast cancer patient depends on both patient related factors and tumour related factors.

In the future we are moving towards increasing personalization of breast cancer therapies.