HORMONAL THERAPY OF BREAST CANCER:
2003 UPDATE

HARMESH NAIK, MD.

OCTOBER 29, 2003
Breast cancer case burden

- Over 200,000 new cases each year in US
- Estimated 2 million women are living with current or previous diagnosis
ER-PR receptors in breast cancer

• Estimated 60% pre-menopausal BCa are positive
• Estimated 75% post-menopausal BCa are positive
• Hormonal therapy is primarily effective in ER/PR positive patients
• True ER/PR negative pts rarely benefit from hormonal therapy
Estrogen receptor

- A major signaling pathway for breast cancer cell proliferation
Estrogen receptor

http://press2.nci.nih.gov/sciencebehind/estrogen/estrogen05.htm
Estrogen receptor function

- Part of nuclear receptor family
- Conformation change after estradiol binding, dissociates HSP 90
- Then, dimerizes and localizes in nucleus
- Binds to DNA responsive elements (ERE)
- Interaction of two co-activators, AF1, AF2 and transcription factors activate RNA polymerase and transcriptional complex
ESTRADIOLE MECHANISM OF ACTION

E-ER DIMERIZATION

ER

AF1

AF2

HSP 90

Co activator 1

Co activator 2

ERE

RNA POLY II

Transcription

Slide prepared by Harmesh Naik, MD.
ER receptor interaction with DNA

The Theoretical and Computational Biophysics Group (TCBG)
an NIH Resource for Macromolecular Modeling and Bioinformatics
http://www.ks.uiuc.edu/Research/pro_DNA/ster_horm_rec/dbd/
ER inhibition (inhibiting estrogen signaling pathways)

- ER receptor blockade
- Blocking estrogen production
- Receptor down regulation/degradation
Classes of drugs

- SERM (Selective estrogen receptor modulators) e.g.. Tamoxifen (TAM), Toremifien, Raloxifen
- Aromatase inhibitors e.g.. Anastrozole (A), Letrozole (L), Exemestane (E)
- Estrogen receptor down regulators e.g.. Fulvestrant (F)
TAMOXIFEN MECHANISM OF ACTION

AF1 explains partial agonist activity
Co activator 1

AF1 explains partial agonist activity
Co activator 1

T-ER DIMERIZATION
AF 2 is inactive

HSP 90

RNA POLY II

Slide prepared by Harmesh Naik, MD.
The estrogen receptor and TAM binding

The estrogen-binding domain (blue)
Associated activation domain AF-2 (green)
Estradiol binds deep within a pocket

Tamoxifen (in pink)
The receptor loop is not able to adopt its active conformation

David S. Goodsell
The Oncologist, Vol. 7, No. 2, 163-164, April 2002

http://theoncologist.alphamedpress.org/cgi/content/full/7/2/163
Tamoxifen and ER

Aromatase inhibition
Fulvestrant mechanism

F-ER DIMERIZATION
Is less

HSP 90

Degraded receptor

Reduced ERE binding

RNA POLY II

Slide prepared by Harmesh Naik, MD.
Hormone therapy for breast cancer

- Proven benefits in
  - Metastatic disease
  - Adjuvant setting
  - DCIS
  - Prevention of breast cancer
Development of hormone therapy in breast cancer

- Metastatic disease
  - Adjuvant therapy
  - DCIS
  - Prevention
Metastatic disease
(Post menopausal)
Post-menopausal Estrogen Source

- Primary source of estrogen is non-ovarian
- Adipose tissue, skin, muscle, adrenal glands
- Through Aromatase enzyme
- Ovarian ablation not useful, but adrenalectomy was useful
MBC: Old standard of care

FIRST LINE: TAMOXIFEN

SECOND LINE: MEGESTROL

THIRD LINE: AMINOGLUTETHEMIDE
MBC: Tamoxifen

• TAM was gold standard for 25 years
  – OR: 30%, additional SD: 20%
  – ER positive RR: 50%
  – Median DOR: 12 months
  – Median survival 2-3 years

• Toremifene
  – similar efficacy data in direct comparison to TAM
  – Used less frequently
MBC: Tamoxifen

• Protective for bones and lipids
• Limitations from Partial agonist activity
  – Uterine cancer risk
  – Thromboembolism risk
• Limitations from antagonist activity
  – CNS effects: Hot flashes
  – Vaginal symptoms
• Better therapy was needed
Aromatase inhibitors (AI)

• First generation AI – Aminoglutethemide
  – Effective but toxic
  – Non-specific AI inhibitor
  – Also inhibits adrenal steroids-requiring steroid replacement

• Second generation AI-Formestane
  – Injectable-not available in US
  – Incomplete estrogen synthesis suppression
Aromatase inhibitors (AI)

• Third generation AIs: Inhibits only androgen to Estrogen conversion
• No need for cortical steroid replacement
• Steroidal AIs (inactivators)
  – Irreversible enzyme inhibition
  – Exemestane (E)
• Non-steroidal AIs
  – Reversible enzyme inhibition
  – Anastrozole (A), Letrozole (L)
## MBC-2nd line trials vs Megestrol (M) Post-menopausal

<table>
<thead>
<tr>
<th>trial</th>
<th>RR/CB</th>
<th>survival</th>
<th>toxicity</th>
<th>author</th>
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<tr>
<td>E vs M</td>
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<td>E better</td>
<td>E less</td>
<td>Kaufman</td>
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<tr>
<td>L vs M</td>
<td>same</td>
<td>NS</td>
<td>L less</td>
<td>Dombernowsky</td>
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MBC-2nd line-new agent comparisons
Post-menopausal

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<tr>
<td>L vs A</td>
<td>Same, ??L&gt;A</td>
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<td>Med TTP (m)</td>
<td>Survival</td>
<td>Toxicity</td>
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<tr>
<td>A vs T Bonneterre</td>
<td>same</td>
<td>A better 10.7 vs 6.4</td>
<td>same</td>
<td>A &lt; DVT, ECa, &gt; fractures</td>
</tr>
<tr>
<td>L vs T Mouridsen</td>
<td>L better 32 vs 21%</td>
<td>L better 9.4 vs 6</td>
<td>Same at 32 mos</td>
<td>L &gt; fractures</td>
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<tr>
<td>F vs T Robertson</td>
<td>RR same</td>
<td>same</td>
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</table>
MBC-3nd line-phase II trials
Post-menopausal

• Exemestane after TAM and M (Jones S)
  – 30% CB

• Exemestane after non-steroidal AI failure (Lonning PE)
  – 24% CB

• Fulvestrant after TAM and an AI (Perey L)
  – 41% CB
  – Early results only
Sequencing of therapy

- Hormonal agents such as TAM, F, AIs maintain effectiveness when used after other hormonal agents.
Metastatic disease
(Pre menopausal)
Pre-menopausal: Estrogen Source

- Primary source of estrogen is ovarian
- Estrogen deprivation by bilateral oophorectomy or medical therapies can lead to regression of BCa
- AIs do not stop ovarian estrogen production and are not considered useful in pre-menopausal women
Pre-menopausal ER/PR positive MBC/advanced BCa

• Ovarian ablation options
  – Surgical castration
  – Ovarian radiation
  – Chemotherapy
  – LHRH agonists (medical castration)
Pre-menopausal ER/PR positive MBC/advanced BCa

- LHRH agonist + TAM vs TAM
- Meta-analysis (Klijn JG)
  - Survival benefit (HR 0.78)
  - Better PFS (HR 0.70)
  - Higher ORR (odds ratio 0.67)
- G = oophorectomy
- Goserelin available in US
- Buserelin not available in US
MBC: Expected objective response rates

FIRST LINE: 20-55%

SECOND LINE: 12-20% range

THIRD LINE: 10% range

Stable disease may be seen in more patients
TTP and survival data

• First line
  – Median TTP 6-10 months
  – Median survival 30-41 months

• Second line
  – Median TTP 3-6 months
  – Median survival 21-28 months
EBC: Adjuvant therapy
Post menopausal
Early breast cancer (EBC): Adjuvant: ATAC trial

3125 patients

TAM x 5 years

A x 5 years

A + T x 5 years
EBC: ATAC trial

• 1st analysis at median f/u of 33.3 months
• A had better DFS (89.4 vs 87.4%)
• A+T no better than TAM (closed)
• In ER positive DFS was significantly longer with A than TAM (HR 0.78)
• Fewer contra-lateral BCa in A group (odds 0.42)
EBC: ATAC trial

• 2nd analysis at median f/u of 47 months
• Results were maintained
  – A had better DFS (86.9 vs 84.5%) and better toxicity profile than TAM
  – In ER positive DFS was significantly longer (89 vs 86.1%) than TAM
  – Fewer contra lateral BCa in A group
• A had less DVT/PE and endometrial cancers,
• However, A group had more fractures
EBC: ATAC trial, 47 month analysis
Disease free survival

84.5
86.1
86.9
89
82
83
84
85
86
87
88
89

T
A

overall
ER pos
EBC: ATAC trial toxicity profile

- Anastrozole profile better
  - Endometrial cancer
  - Hot flashes
  - Thromboembolism
  - Vaginal symptoms
  - Weight gain

- Tamoxifen profile better
  - Musculoskeletal events
  - Fractures
ASCO committee report

• TAM still standard of care
• ATAC results promising
• Individual providers and patients may reach their own conclusion of data

• Above was based on initial analysis
FDA approval

• FDA approved A for adjuvant use in post-menopausal women
When change from TAM to A

- Patient request
- TAM side effects
- Concerns regarding TAM risk factors
NCIC Letrozole trial

NCIC Letrozole trial

- Median follow up 2.4 years
- Stopped early as per monitoring committee recommendations
- None of the patients received planned 5 years of L, only 1% received 4 years of L
- Median duration of therapy is only 3 years

NCIC Letrozole trial-interim analysis

NCIC Letrozole trial-Estimated 4 year Disease free and overall survival

NCIC Letrozole trial: Efficacy

- L is better than Placebo (HR 0.57)
- Better rates of
  - Local-regional recurrence
  - Distant recurrence
  - Contra-lateral breast cancer
- Magnitude of benefit (estimated) at 3 yrs
  - 5% absolute improvement in DFS
  - 43% relative reduction in rec or new primary

NCIC Letrozole trial: Editorial

• Editorial by John Bryant et al. in NEJM 349:19, November 6, 2003.
• “At a minimum, suitable patients must be apprised of the these important observations and must be given the opportunity to receive Letrozole, with an understanding of the limitation of the data”.

NCIC Letrozole trial: Toxicity

- **L (4.5% discontinued study)**
  - Hot flashes
  - Arthralgia, arthritis, myalgia
  - Trend towards more osteoporosis (NS)
  - Slightly more cardio-vascular event (NS)
- **Placebo (3.6% discontinued study)**
  - Vaginal bleeding
  - Fractures

Concerns for AI use in EBC

- Direct cost: twice as much as TAM
- Side effects
  - Osteoporosis/fractures
  - ?? ?? Cognition
  - Lipids: Early data is favorable
- Long term follow-up is needed
- Duration needs to be better defined
- Sequencing needs to be defined
EBC: Adjuvant therapy
Pre menopausal
Pre-menopausal ER/PR positive EBC

- TAM in overview analysis
  - 45% reduction in recurrence risk
  - 32% reduction in risk of death

- Ovarian ablation
  - Improves 15 year DFS
  - Improves 15 year OS

- Goserelin (G) may be a valuable agent
Pre-menopausal ER/PR positive EBC

• ZEBRA trial (Jonat W.):
  – Goserelin vs CMF
  – Same DFS and OS in ER/PR positive

• INT 0101 trial (Davidson N)
  – CAF vs CAF+G vs CAF+G+TAM
  – CAF+G+TAM had best outcome and lowest new primaries
Summary
## Summary of hormonal therapy based on menopausal status

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre-menopausal</th>
<th>Post-menopausal</th>
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<tbody>
<tr>
<td>Ovarian ablation</td>
<td>Effective</td>
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<tr>
<td>Tamoxifen</td>
<td>Effective</td>
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<td>Megestrol</td>
<td>Effective</td>
<td>Effective</td>
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<td>AI</td>
<td>Not effective</td>
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<tr>
<td>SEDR</td>
<td>??????</td>
<td>Effective</td>
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</table>
Post menopausal MBC summary: acceptable therapy choices

• First line
  – A, L, TAM, ??F
• Second line
  – A, L, E, TAM, F
• Third line
  – Tam, E, F
• Fourth line
  – M, Tam
MBC-treatment paradigm shift
Post-menopausal

<table>
<thead>
<tr>
<th>MBC</th>
<th>1\textsuperscript{st} line</th>
<th>2\textsuperscript{nd} line</th>
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<tbody>
<tr>
<td>Old std</td>
<td>TAM</td>
<td>MEG</td>
<td>AG</td>
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<tr>
<td>AI/SERD 2\textsuperscript{nd} line</td>
<td>TAM</td>
<td>\underline{A/L/E , A=F}</td>
<td>MEG</td>
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<td>\underline{A/L}</td>
<td>??F</td>
<td>TAM/E</td>
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<td>TAM=F</td>
<td>??Al</td>
<td>\underline{E, F}</td>
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*Underline indicates availability of recent phase III data*
Pre-menopausal ER/PR positive MBC : acceptable therapy choices

• First line
  – TAM, Ovarian ablation

• Second line
  – TAM, M

• Third line
  – Aminoglutethemide
Adjuvant-treatment paradigm shift
Post-menopausal ER/PR positive

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<th>Adjuvant</th>
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<th>+5 years</th>
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<tr>
<td>Old + current std TAM</td>
<td>-</td>
<td>--</td>
</tr>
<tr>
<td>Current std A</td>
<td>-</td>
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</tr>
<tr>
<td>Current std T L</td>
<td>L</td>
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Underline indicates availability of recent phase III data
## Adjuvant-treatment paradigm shift
### Pre-menopausal ER/PR positive

<table>
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<th>Current std</th>
<th>Adjuvant therapy</th>
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<tr>
<td></td>
<td>TAM x 5 years</td>
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<td>?? G x 2 years</td>
</tr>
</tbody>
</table>
|             | ?? G + TAM x 5 years  
with chemotherapy |

*Underline indicates availability of recent phase III data*
Additional review references

- NEJM website.
- V. Craig Jordan: Endo rev 20 (3): 253-278.
THANK YOU FOR YOUR ATTENTION!