BREAST CANCER: ENDOCRINE THERAPY

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General Principles of Therapy

- chemotherapy benefits everyone
- endocrine therapy benefits only those with hormone receptor positive disease
ENDOCRINE THERAPY: GENERAL PRINCIPLES
Overview

• The response to endocrine therapy correlates with hormone receptor status.
Overview

- Estrogen receptor positivity varies according to menopausal status.

(Hormone Receptor Status) (Beck WW. Obstetrics and Gynecology. 1989.)
Overview

• The choice of a particular endocrine agent is dictated by the primary site of estrogen production.
DRUG OVERVIEWS
Approach to Therapy

• The goal is to minimize interactions between estrogen and its receptor.
  - reduce the synthesis of estrogen
  - interfere with estrogen activity at the level of the tumor cell
Endocrine Therapy: Mechanisms

(Clarke et al. Oncogene 2003. 22:7316.)
Endocrine Therapy: History

- 1900: Oophorectomy
- 1925: Ovarian ablation by irradiation
- 1950: High-dose estrogens and androgens vs. adrenalectomy vs. hypophysectomy
- 1975: FDA approves tamoxifen
- 2000: FDA approves anastrozole
Classes of Hormonal Agents

- sex steroids
- estrogen receptor modulators
- aromatase inhibitors
- pure anti-estrogens
- LHRH agonists
Sex Steroids

- megestrol acetate (Megace)
- fluoxymesterone (Halotestin)
- estrogen
Sex Steroids: Megestrol Acetate

- potential toxicities:
  - vasomotor instability
  - weight gain and/or fluid retention
  - gastrointestinal disturbance
  - thromboembolic phenomena
  - hypertension, cardiomyopathy
  - hyperglycemia, adrenal suppression
Sex Steroids: Fluoxymesterone

- potential toxicities:
  - acne
  - facial hair growth
  - weight gain and/or fluid retention
  - change in libido
  - cardiomyopathy
  - polycythemia
Classes of Hormonal Agents

- sex steroids
- estrogen receptor modulators
- aromatase inhibitors
- pure anti-estrogens
- LHRH agonists
Estrogen Receptor Modulators

- tamoxifen (Nolvadex)
- toremifene (Farnesdon)
- raloxifene (Evista)
Estrogen Receptor Modulators: Tamoxifen

• potential toxicities:
  - vasomotor instability
  - vaginal discharge, atrophic vaginitis
  - weight gain
  - thromboembolic phenomena
  - liver function abnormalities
  - uterine hyperplasia or cancer
  - early cataract development
Estrogen Receptor Modulators: Tamoxifen

- other potential benefits (postmenopausal women):
  - protection against osteoporosis
  - improvement in the lipid profile
Classes of Hormonal Agents

- sex steroids
- estrogen receptor modulators
- aromatase inhibitors
- pure anti-estrogens
- LHRH agonists
Aromatase Inhibitors

**Nonsteroidal Inhibitors**
- anastrozole (Arimidex)
- letrozole (Femara)

**Steroidal Inactivators**
- exemestane (Aromasin)
Aromatase Inhibitors

- potential toxicities:
  - vasomotor instability
  - asthenia
  - musculoskeletal pain
  - gastrointestinal upset
  - vaginal discharge, atrophic vaginitis
  - accelerated bone density loss
Classes of Hormonal Agents

- sex steroids
- estrogen receptor modulators
- aromatase inhibitors
- pure anti-estrogens
- LHRH agonists
Pure Anti-Estrogens

- fulvestrant (Faslodex)
Pure Anti-Estrogens: Fulvestrant

- potential toxicities:
  - vasomotor instability
  - peripheral edema
  - musculoskeletal pain
  - gastrointestinal upset
  - pain at the injection site
  - thromboembolic phenomena
  - bone marrow suppression
Classes of Hormonal Agents

- sex steroids
- estrogen receptor modulators
- aromatase inhibitors
- pure anti-estrogens
- LHRH agonists
LHRH Agonists

- goserelin (Zoladex)
- leuprolide (Lupron)
LHRH Agonists

• potential toxicities:
  - accelerated bone density loss
  - vasomotor instability
  - atrophic vaginitis
  - emotional lability
  - arthralgias
COMPARISON OF TOXICITIES
### SERM's vs. Progestins

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen</th>
<th>Raloxifene</th>
<th>Megestrol</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Weight Gain</td>
<td>X</td>
<td>X</td>
<td>XXXXXXX</td>
</tr>
<tr>
<td>Hot Flashes</td>
<td>XX</td>
<td>X</td>
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</tr>
<tr>
<td>Thrombosis</td>
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<td>XX</td>
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<tr>
<td>Altered Mood</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Edema</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Vaginal Discharge</td>
<td>XX</td>
<td>XX</td>
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<tr>
<td>Arthralgias</td>
<td>X</td>
<td>X</td>
<td>XX</td>
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<tr>
<td>Uterine Changes</td>
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# Tamoxifen vs. AI’s

<table>
<thead>
<tr>
<th>Symptom</th>
<th>tamoxifen</th>
<th>anastrozole</th>
<th>letrozole</th>
<th>exemestane</th>
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<tbody>
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<td>nausea</td>
<td>X</td>
<td>XX</td>
<td>X</td>
<td>X</td>
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<tr>
<td>weight gain</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>hot flashes</td>
<td>XX</td>
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<tr>
<td>thrombosis</td>
<td>XX</td>
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<td>none</td>
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</tr>
<tr>
<td>altered mood</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>none</td>
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<td>XX</td>
<td>X</td>
<td>X</td>
<td>none</td>
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<tr>
<td>arthralgias</td>
<td>X</td>
<td>XXX</td>
<td>XXX</td>
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<td>uterine changes</td>
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# Tamoxifen vs. Other

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen</th>
<th>Fulvestrant</th>
<th>LHRH Agonists</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>X</td>
<td>XX</td>
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<tr>
<td>Weight Gain</td>
<td>X</td>
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<td>Hot Flashes</td>
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INDICATIONS
Adjuvant Therapy for Early Stage Breast Cancer: All Patients
Tamoxifen: The EBCTCG Meta-Analysis

• 55 trials with 37,000 women

• stage I-II breast cancer

• benefits in ER+ or unknown disease only
**Tamoxifen vs. Not:**
The EBCTCG Meta-Analysis

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>2 years</th>
<th>5 years</th>
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<tbody>
<tr>
<td>proportional reduction in risk of recurrence</td>
<td>21%</td>
<td>28%</td>
<td>50%</td>
</tr>
<tr>
<td>proportional reduction in mortality</td>
<td>14%</td>
<td>18%</td>
<td>28%</td>
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(EBCTCG. Lancet 1998. 351:1451.)
Tamoxifen: EBCTCG Analysis

Recurrence

- Control: 45.0%
- About 5 years of tamoxifen: 33.2%
- 15-year gain 11.8% (SE 1.3)
- Logrank 2p<0.00001

Breast cancer mortality

- Control: 34.8%
- About 5 years of tamoxifen: 25.6%
- 15-year gain 9.2% (SE 1.2)
- Logrank 2p<0.00001

(EBCTCG. Lancet 2005. 365:1687.)
Tamoxifen: Beyond 5 Years

- Do the beneficial effects persist beyond the first five years of treatment?

- Is >5 years of tamoxifen better?
Tamoxifen: NSABP B-14

N = 1172

HR positive postmenopausal
tamoxifen x 5 years

(second randomization)

tamoxifen x 5 years

placebo x 5 years
# Tamoxifen: NSABP B-14

<table>
<thead>
<tr>
<th></th>
<th>10 year course</th>
<th>5 year course</th>
<th>( p )</th>
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</thead>
<tbody>
<tr>
<td>7 year - DFS</td>
<td>78%</td>
<td>82%</td>
<td>0.03</td>
</tr>
<tr>
<td>7 year - OS</td>
<td>91%</td>
<td>94%</td>
<td>0.07</td>
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Adjuvant Therapy for Early Stage Breast Cancer: Postmenopausal Patients
New Standards?

• instead of tamoxifen
  - anastrozole
  - letrozole

• in sequence with tamoxifen
  - letrozole
  - exemestane
  - anastrozole
### New Endocrine Strategies

<table>
<thead>
<tr>
<th>Initial Therapy</th>
<th>TAMOXIFEN</th>
<th>AROMATASE INHIBITOR</th>
</tr>
</thead>
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<tr>
<td>ATAC, BIG 1-98</td>
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</table>

<table>
<thead>
<tr>
<th>Sequential Therapy</th>
<th>TAMOXIFEN × 2-3 years</th>
<th>TAMOXIFEN</th>
<th>AROMATASE INHIBITOR</th>
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<tbody>
<tr>
<td>ABCSG 8, ARNO 95, ITA, IES</td>
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<table>
<thead>
<tr>
<th>Initial vs. Sequential Therapy</th>
<th>TAMOXIFEN</th>
<th>AROMATASE INHIBITOR</th>
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<td>TEAM</td>
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<table>
<thead>
<tr>
<th>Initial vs. Sequential Therapy</th>
<th>TAMOXIFEN</th>
<th>AROMATASE INHIBITOR</th>
<th>TAMOXIFEN</th>
<th>AROMATASE INHIBITOR</th>
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<td>BIG 1-98</td>
<td>**</td>
<td></td>
<td>**</td>
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</tbody>
</table>

* Asterisks indicate statistical significance.
New Endocrine Strategies

extended sequential therapy

* 

tamoxifen x 5 years

aromatase inhibitor

placebo

MA 17, ABCSG-6A, NSABP B-33
New Endocrine Strategies

<table>
<thead>
<tr>
<th>absolute DFS reductions at longest follow-up</th>
<th>initial</th>
<th>5 year sequential</th>
<th>extended sequential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-5%</td>
<td>3-5%</td>
<td>6%</td>
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</table>
Additional Benefits with Aromatase Inhibitors

- decreased risk of contralateral disease
- no negative effects on the endometrium
- minimal risk of thromboembolic events
Additional Risks with Aromatase Inhibitors

- accelerated bone mineral density loss
- arthralgias and/or myalgias
- alterations in the lipid profile
- increased risk of cardiovascular disease
Adjuvant Therapy for Early Stage Breast Cancer: Premenopausal Patients
New Standards?

- ovarian functional suppression . . .
  - instead of chemotherapy
  - instead of tamoxifen
  - with tamoxifen
  - with an aromatase inhibitor
SOFT

definitive surgery

- OR-

definitive surgery then chemotherapy

- OR-

- OR-

tamoxifen x 5 years

OFS and tamoxifen x 5 years

OFS and exemestane x 5 years
PERCHE

- definitive surgery
- chemotherapy + OFS + tamoxifen or exemestane
- OFS + tamoxifen or exemestane
definitive surgery

OFS + tamoxifen

OFS + exemestane
Metastatic Breast Cancer: All Patients
General Principles

• expected responders: 50-60%

• duration of response: 8-14 months
Guiding Principles

<table>
<thead>
<tr>
<th>Endocrine therapy</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td>• hormone receptor positive</td>
<td>• hormone receptor negative</td>
</tr>
<tr>
<td>• long disease free interval *</td>
<td>• short disease free interval *</td>
</tr>
<tr>
<td>• bone/soft tissue disease</td>
<td>• extensive visceral disease</td>
</tr>
<tr>
<td>• sensitive to endocrine therapy</td>
<td>• refractory to endocrine therapy</td>
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(* defined in relation to a two year interval from initial diagnosis)
## Tamoxifen: Advanced Disease

<table>
<thead>
<tr>
<th></th>
<th>postmenopausal</th>
<th>premenopausal</th>
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<tbody>
<tr>
<td><strong>objective response rates</strong></td>
<td>15-53%</td>
<td>20-45%</td>
</tr>
<tr>
<td><strong>duration of response</strong></td>
<td>20 months</td>
<td>≤36 months</td>
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</table>
Metastatic Breast Cancer: Postmenopausal Patients
Aromatase Inhibitors

- **anastrozole**
  - vs. megestrol: improved survival
  - vs. tamoxifen: longer time to progression

- **letrozole**
  - vs. megestrol: no difference
  - vs. tamoxifen: longer time to progression
  - vs. anastrozole: no difference
Aromatase Inhibitors

- exemestane
  - vs. megestrol: longer time to progression
  - vs. tamoxifen: no difference
Pure Antiestrogens

- fulvestrant
  - vs. anastrozole: no difference
  - vs. exemestan: no difference
Treatment Algorithm

tamoxifen
nonsteroidal aromatase inhibitor
pure anti-estrogen
steroidal aromatase inhibitor
megestrol acetate
androgen or aminogluthethimide
Metastatic Breast Cancer: Premenopausal Patients
Ovarian Functional Suppression

• Small randomized trials suggest that the combination of ovarian functional suppression and tamoxifen may be superior to tamoxifen alone.
Treatment Algorithm

tamoxifen or LHRH Agonist
LHRH Agonist or Tamoxifen
oophorectomy
nonsteroidal aromatase inhibitor
pure anti-estrogen
steroidal aromatase inhibitor
megestrol acetate
androgen or aminoglutethimide
TAKE HOME POINTS
Tamoxifen is effective for patients with hormone receptor positive breast cancer, irrespective of their menopausal status.
The nonsteroidal aromatase inhibitors have demonstrated equivalence or superiority to tamoxifen in the management of postmenopausal women.
Ovarian suppression (or ablation), alone or in combination with tamoxifen, may be equivalent or superior to chemotherapy in the treatment of premenopausal women.
We have a great deal more to learn with respect to the biology of breast cancer...
THANK YOU