Hormonal Therapy of Breast Cancer

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Characteristics of Hormone Dependent Breast Cancer

- Functional ER/PR
- Histologic differentiation
- Low S phase, diploid
- Long disease-free interval
- Metastasis to favorable sites
- Indolent clinical course
- More prevalent in older patients
- Sequential responses to endocrine therapies
Sequential Response to Hormonal Therapy

First Line 40%  Second Line 30%  Third Line 25%  Fourth Line 15%

Number of Breast Cancer Patients Eligible for Therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Eligible Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced premenopausal/ER+</td>
<td>41,700</td>
</tr>
<tr>
<td>Advanced premenopausal/ER−</td>
<td>19,000</td>
</tr>
<tr>
<td>Advanced postmenopausal/ER+</td>
<td>200,800</td>
</tr>
<tr>
<td>Advanced postmenopausal/ER−</td>
<td>28,800</td>
</tr>
<tr>
<td>Early premenopausal/ER+</td>
<td>140,400</td>
</tr>
<tr>
<td>Early premenopausal/ER−</td>
<td>29,700</td>
</tr>
<tr>
<td>Early postmenopausal/ER+</td>
<td>509,600</td>
</tr>
<tr>
<td>Early postmenopausal/ER−</td>
<td>59,700</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,029,700</strong></td>
</tr>
</tbody>
</table>

US and Europe Approximation.
Current Endocrine Therapies for Breast Cancer

- Ovarian ablation
  - Surgical (oophorectomy)
  - Radiation
- LHRH agonists
- Antiestrogens
- Aromatase inhibitors (nonselective and selective)
- Progestins
- Androgens
- Others: estrogens, pure antiestrogens, LHRH antagonists, glucocorticoids

Hormonal Treatment of Advanced Breast Cancer

GnRH Agonists

(A) Premenopausal
  LH
  FSH
  Estrogen
  Antiestrogen

(B) Postmenopausal
  Estrogen
  Androstenedione
  Aromatase Inhibitor
  Peripheral Aromatization

Hormone Dependent Breast Carcinoma

Cytoplasm

E₂

E₂

E₂ + ER

E₂·ER

PgR mitosis

Chromatin

RNA

Nucleus

E₂ = Estradiol
ER = Estrogen receptor
E₂·ER = Estradiol-receptor complex
PgR = Progesterone receptor

Estrogen Receptor Function

Receptors

Receptor-Interacting Proteins

TAFs

SERMs

E₂

Tam

Ral

ERα

ERβ

Coactivators

Corepressors

REs

Transcription

mRNA

Promoters

Target Genes
Breast Cancer Disease Progression

*Note: 90 day doubling x 40 doublings = 3,600 days (approximately 10 years).

The Breast Cancer Continuum
Role of Antiestrogens

Normal  →  Chemoprevention
Premalignant  →  DCIS
Primary cancer  →  Neoadjuvant
Postsurgery  →  Adjuvant
Metastatic  →  Palliative
Alternatives After Antiestrogen Therapy

Blockade of estrogen receptor (antiestrogen therapy)

Inhibition of estrogen synthesis (aromatase inhibition)

? Same or better

Estrogen Biosynthetic Pathway

Androstenedione \[\xrightarrow{17\text{ HSD}}\] Testosterone

\[\xrightarrow{\text{Aromatase}}\] Estrone

\[\xrightarrow{17\text{ HSD}}\] Estradiol
The Role of Aromatase in Estrogen Biosynthesis and Tumor Growth

Adrenal Gland → Peripheral Tissues

Androstenedione → Tumor

Antiaromatase Agents: Mechanism of Action

Cholesterol → Pregnenolone → Cortisol

Progesterone → Androstenedione → Testosterone

Aromatase Inactivators and Aromatase Inhibitors

Estrogen Estrogen
Development of Aromatase Inhibitors

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Specificity</th>
<th>Potency</th>
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</thead>
<tbody>
<tr>
<td>Rash, etc.</td>
<td>No adrenal insufficiency, etc.</td>
<td>1,000 to 10,000</td>
</tr>
</tbody>
</table>

Aminoglutethimide
- First generation

Fadrozole
- 4-OHA
- Second generation

Anastrozole
- Exemestane
- Letrozole
- Third generation

Differences in Structure of Antiaromatase Agents

Nonsteroidal Inhibitors
- Aminoglutethimide
- Letrozole
- Anastrozole

Steroidal Inactivators
- Exemestane
- Formestane

Androgen Substrate
- Androstenedione
Quality of Life in Patients With Metastatic Breast Cancer

- Metastatic breast cancer cannot be cured
- Quality of life and duration of remission are the most important parameters of therapeutic success in women with advanced disease
- Aromatase inhibitors offer an option for postmenopausal women who no longer respond to antiestrogen therapy
- Aromatase inhibitors (eg, letrozole) are as effective as progestins (eg, megestrol acetate) as second-line therapy, but have better side-effect profiles, offering improved quality of life

Antiaromatase Agents Versus Megestrol Acetate (MA)

<table>
<thead>
<tr>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arimidex®</td>
<td>Femara®</td>
<td>Aromasin®</td>
</tr>
<tr>
<td>1 mg</td>
<td>2.5 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>versus MA</td>
<td>versus MA</td>
<td>versus MA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>AN = MA</th>
<th>LET &gt; MA</th>
<th>EXE = MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>263 vs 253</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CR + PR, %</th>
<th>AN = MA</th>
<th>LET &gt; MA</th>
<th>EXE &gt; MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>263 vs 253</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration clinical benefit</th>
<th>AN = MA</th>
<th>LET &gt; MA</th>
<th>EXE &gt; MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Reported</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TTP</th>
<th>AN = MA</th>
<th>LET = MA</th>
<th>EXE &gt; MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Reported</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TTF</th>
<th>AN &gt; MA</th>
<th>LET = MA</th>
<th>EXE &gt; MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Pooled Data)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* >, Difference statistically significant in favor of first agent.
=, Difference not statistically significant.
Aromatase Inhibitors: Rationale for First-Line Use

- Selective Als, anastrozole and letrozole, represent a significant advantage over existing second-line endocrine therapies in postmenopausal women with advanced breast cancer
- Rapidly becoming established as the treatments of choice in this patient population
- These results provide a rationale for studying aromatase inhibitors as first-line endocrine therapy

First-Line Trials of Anastrozole Versus Tamoxifen (027 and 030): Randomization

Randomized 1:1 (double blind, double dummy)

- Anastrozole 1 mg/day plus tamoxifen placebo daily
- Tamoxifen 20 mg/day plus anastrozole placebo daily

For study endpoints

- Objective progression
- Treatment may stop/standard treatment initiated

Patients followed for death details
Hormonal Therapy

**Time to Progression: Combined Results From Trials 027 and 030**

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole</th>
<th>Tamoxifen</th>
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<tbody>
<tr>
<td>Median TTP</td>
<td>259 days</td>
<td>212 days</td>
</tr>
<tr>
<td>CR + PR</td>
<td>29.0%</td>
<td>27.1%</td>
</tr>
<tr>
<td>CR + PR + SD</td>
<td>57.1%</td>
<td>52.0%</td>
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</tbody>
</table>


**Anastrozole as First-Line Therapy for Advanced Breast Cancer: Summary**

- At least as effective as tamoxifen (time to progression and objective response)
- Fewer thromboembolic events and less vaginal bleeding
- First aromatase inhibitor to demonstrate at least equivalence to tamoxifen
Letrozole
Oral Nonsteroidal Aromatase Inhibitor

\[4,4'-(1H-1,2,4-triazol-1-yilmethylene)-bis-benzonitrile\]

Action of Femara on Estrogen Biosynthesis

- Adrenal Gland
- Peripheral Tissues

○ = Estrogen
□ = Androstenedione
Tumor
Postmenopausal women

\(\text{Femara} \rightarrow \text{Aromatase} \rightarrow \text{Estrogen} \)
Breast Cancer
Sequential Use of Hormones

Prevention
Tam?
Diet?
Retinoids?

Adjuvant
Tamoxifen

First line
Aromatase inhibitors
Letrozole

Second line
Pure antiestrogen

Third line
Progestin

Resistance

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