Treatment of Metastatic Breast Cancer: Endocrine Therapies

Robert W. Carlson, M.D.
Professor of Medicine
Stanford University
MDACC Experience with FAC in Chemotherapy-Naive MBC

Greenberg et al, J Clin Oncol 1996
TREATMENT OF RECURRENCE/STAGE IV DISEASE

Initial treatment with mastectomy → Surgical resection (if possible) + radiation therapy (if possible) → Consider systemic therapy

Local recurrence

Initial treatment with lumpectomy + radiation therapy → Mastectomy → Consider systemic therapy
Biological Approach to Advanced Breast Cancer

- Advanced Breast Cancer
  - ER and/or PR Positive
    - Endocrine Therapy
      - Refractory to Endocrine Therapy
  - ER and PR Negative
    - HER2 Positive
      - Trastuzumab +/- Chemotherapy
      - Lapatinib + Chemotherapy
    - HER2 Negative
      - Chemotherapy
  - Refractory to Endocrine Therapy
Invasive Breast Cancer
Clinical Practice Guidelines in Oncology – v2.2008

TREATMENT OF RECURRENT/STAGE IV DISEASE

Systemic disease

Bone disease present

Add bisphosphonate

ER and/or PR positive; HER2 negative

ER and/or PR positive; HER2 positive

ER and PR negative, or ER and/or PR positive and endocrine refractory; HER2 negative

ER/PR negative; HER2 positive

See BINV-17

See BINV-18

See BINV-19

Bone disease not present
TREATMENT OF RECURRENCE/STAGE IV DISEASE

ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE

Prior endocrine therapy within 1y

*Premenopausal*

Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women

*Postmenopausal*

Visceral crisis

Consider initial chemotherapy

ER and/or PR positive; HER2 negative

No prior endocrine therapy within 1y

Premenopausal

Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women or Antiestrogen

Postmenopausal

Aromatase inhibitor or Antiestrogen

Visceral crisis

Consider initial chemotherapy
ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.

BY GEORGE THOMAS BEATSON, M.D. EDIN., SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON, GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH.

I have no doubt it has fallen to the lot of nearly every medical man to have been consulted from time to time by patients suffering from carcinoma so widely spread or so situated that it has been quite apparent that nothing in the way of operative measures could be recommended. Such cases naturally excite our sympathy, but they also bring home to us the fact that once a case of cancer has passed beyond the reach of surgical intervention...
<table>
<thead>
<tr>
<th>Receptor Status</th>
<th>Likelihood of Tumor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+, PR+</td>
<td>50-75%</td>
</tr>
<tr>
<td>ER+, PR-</td>
<td>20-30%</td>
</tr>
<tr>
<td>ER-, PR+</td>
<td>30-50%</td>
</tr>
<tr>
<td>ER-, PR-</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

ER = Estrogen receptor
PR = Progesterone receptor
### Endocrine Therapies for Breast Cancer

#### Menopausal Status

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian ablation</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>LHRH agonists</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Aromatase inhibitors/inactivators</td>
<td>X</td>
<td>Progestins</td>
</tr>
<tr>
<td>Androgens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER Down-regulators</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

Others: antiprogestins, antiandrogens, somatostatins, glucocorticoids, estrogens.

*X=Not Applicable*
Meta-analysis of LH-RH Agonists +/- Tamoxifen in Metastatic Breast Cancer

- Four studies included
- Total of 506 premenopausal subjects
- Based on individual patient data

Kiljn, 2001
## Results

### LHRH + T vs LHRH

<table>
<thead>
<tr>
<th></th>
<th>LHRH + T</th>
<th>LHRH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>39%</td>
<td>30%</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of response</td>
<td>602 days</td>
<td>350 days</td>
<td></td>
</tr>
</tbody>
</table>

Kiljn, 2001
## Results

**LHRH + T v LHRH**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>0.78 (0.63-0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>0.70 (0.58-0.85)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Kiljn, 2001
Invasive Breast Cancer
Clinical Practice Guidelines in Oncology – v2.2008

TREATMENT OF RECURRENCE/STAGE IV DISEASE
ER and/or PR positive; HER2 negative or positive

- Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women

- Consider initial chemotherapy

ER and/or PR positive; HER2 negative

- Premenopausal
- Postmenopausal
- Visceral crisis

Prior endocrine therapy within 1y

ER and/or PR positive; HER2 positive

- Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women or Antiestrogen

- Aromatase inhibitor or Antiestrogen

- Consider initial chemotherapy

No prior endocrine therapy within 1y

Postmenopausal

Visceral crisis

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Aromatase Inhibitors: Mechanism of Action

- Cholesterol
- Pregnenolone
- Progesterone
- Aldosterone
- Estrone
- Estradiol
- Androstenedione
- Testosterone
- Cortisol
- Pregnenolone
- Androstenedione
- Estrone
- Estradiol
- Testosterone

Aromatase Inactivators and Aromatase Inhibitors
### Aromatase Inhibitors*:
#### Characteristics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Selective</th>
<th>Competitive</th>
<th>Steroidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglutethimide (Cytadren®)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Anastrozole (Arimidex®)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Yes</td>
<td>Yes (No (Femara®))</td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td>Yes</td>
<td>No</td>
<td>Yes (Aromasin®)</td>
</tr>
</tbody>
</table>

*Available in the United States.
Third-Generation AIs in First-Line Studies

Randomize

- Tamoxifen 20 mg
- Third-generation AIs
  - Anastrozole 1 mg
  - or
  - Letrozole 2.5 mg
  - or
  - Exemestane 25 mg
Randomized phase III studies of Aromatase Inhibitors vs Tamoxifen as Initial Therapy of Metastatic Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole</th>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>170 vs 182</td>
<td>340 vs 328</td>
<td>453 vs 454</td>
<td>182 vs 189</td>
</tr>
<tr>
<td>OR, %</td>
<td>21 vs 17</td>
<td>33 vs 33</td>
<td>30 vs 20*</td>
<td>46 vs 31*</td>
</tr>
<tr>
<td>Clin. Benefit, %</td>
<td>59 vs 46*</td>
<td>56 vs 56</td>
<td>49 vs 38*</td>
<td>66 vs 49*</td>
</tr>
<tr>
<td>TTP/PFS, mo</td>
<td>11 vs 6*</td>
<td>8 vs 8</td>
<td>9 vs 6*</td>
<td>10 vs 6*</td>
</tr>
<tr>
<td>ER unknown, %</td>
<td>11 vs 11</td>
<td>56 vs 54</td>
<td>34 vs 33</td>
<td>15 vs 11</td>
</tr>
</tbody>
</table>
Aromatase Inhibitors

- Anastrozole, letrozole, exemestane superior to tamoxifen in 1\textsuperscript{st} line therapy and megestrol acetate as 2\textsuperscript{nd} line therapy.
- Limited toxicity (arthralgias/bone loss).
- Non cross-resistance (reversible and non-reversible).
Goserelin + Anastrozole Trial Schema

- Goserelin 3.6 mg SQ day 1
- Anastrozole 1 mg PO daily beginning day 22
- Goserelin 3.6 mg SQ every 4 weeks
- Monitor disease activity every 3 months
- Estradiol levels at baseline, 1, 3, and 6 months
- All subjects premenopausal with hormone receptor positive, metastatic breast cancer
Rates of Response

Abstract 1030

N = 32

% Response

CR: 3%
PR: 34%
SD 6+ mos: 34%
Clin benefit: 72%
Freedom from Progression and Overall Survival

N = 32

Survival

FFP

Event Free (%)

Time (months)

Abstract 1030
Fulvestrant
(Fasolodex™, ICI 182,780)

- Binds estrogen receptor with high affinity
- Causes estrogen receptor degradation and downregulation

\[
\text{Fulvestrant}
\]

\[
\text{OH}
\]

\[
\text{HO}
\]

\[
\text{(CH}_2\text{)}_9\text{SO(CH}_2\text{)}_3\text{CF}_2\text{CF}_3
\]
Fulvestrant
(Fasolodex™, ICI 182,780)

- A pure estrogen antagonist
- I.M. administration
- No endometrial stimulation
Trial 021
Study Design

Metastatic breast cancer
Postmenopausal
Prior tamoxifen therapy

Fulvestrant
Anastrozole
### Response to Treatment
**Trial 021 (North American Trial)**

#### Number of patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant (n=206)</th>
<th>Anastrozole (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>10 (4.9)</td>
<td>7 (3.6)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>26 (12.6)</td>
<td>27 (13.9)</td>
</tr>
<tr>
<td>Objective response (CR+PR)</td>
<td>36 (17.5)</td>
<td>34 (15.7)*</td>
</tr>
<tr>
<td>Stable disease ≥ 24 weeks</td>
<td></td>
<td>51 (24.8)</td>
</tr>
<tr>
<td>Clinical Benefit (CR + PR + SD ≥ 24 weeks)</td>
<td>87 (42.2)</td>
<td>70 (36.1)</td>
</tr>
</tbody>
</table>

* Odds ratio (95.14 CI) 1.38 (0.84–2.29), \( P=0.20 \)
Time to Progression (TTP)
Trial 021 (North American)

Fulvestrant 250 mg
Anastrozole 1 mg

Hazard ratio (95.14% CI): 0.92 (0.74–1.14); \( P=0.43 \)
Duration of Clinical Benefit (DoCB)
Trial 021 (North American Trial)

Median DoCB:
- Fulvestrant 250 mg: 12.9 months
- Anastrozole 1 mg: 10.8 months
Fulvestrant and exemestane after progression on non-steroidal AIs

<table>
<thead>
<tr>
<th>Endocrine agent</th>
<th>Reference</th>
<th>CBR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant</td>
<td>Ingle et al 2006</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Perey et al 2006</td>
<td>30</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Lønning et al 2000</td>
<td>20</td>
</tr>
</tbody>
</table>

Perey et al, Ann Oncol Advance Access published online on October 9, 2006
Progression

Fulvestrant loading dose + placebo for exemestane (n=330)

Prior non-steroidal AI failure

Exemestane 25 mg orally daily + placebo for Fulvestrant (n=330)

Survival

Analysis after 580 events (progression or death)

Progression

Survival
Time to progression (ITT)

Proportion of patients progression-free

<table>
<thead>
<tr>
<th>Months</th>
<th>Fulvestrant</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>351</td>
<td>342</td>
</tr>
<tr>
<td>3</td>
<td>195</td>
<td>190</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>15</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>18</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>21</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Fulvestrant | Exemestane
Median (months) | 3.7 | 3.7
HR = 0.963, 95% CI (0.819, 1.133), p=0.6531
Cox analysis, p=0.7021

Gradishar, SABCS 2006
### Objective response and clinical benefit rate
(evaluable for response population)

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant</th>
<th>Exemestane</th>
<th>Odds ratio* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR rate (CR + PR)</td>
<td>7.4%</td>
<td>6.7%</td>
<td>1.120 (0.578, 2.186)</td>
<td>0.7364</td>
</tr>
<tr>
<td>CB rate (OR + SD ≥24 wks)</td>
<td>32.2%</td>
<td>31.5%</td>
<td>1.035 (0.720, 1.487)</td>
<td>0.8534</td>
</tr>
</tbody>
</table>

*Analyses are not adjusted for baseline covariates*
Fulvestrant Clinical Trials

1. Similar to aromatase inhibitors in tam-resistant patients.

2. Similar to tamoxifen as first-line therapy.

3. Active post AIs.

4. Minimal side effects.

5. Requires IM administration.

6. Optimal dose and schedule uncertain.
Postmenopausal ER+ Disease
Recurrent or Metastatic Disease

- Tamoxifen, steroidal AIs, non-steroidal AIs, fulvestrant all have similar activity
- Sequence of therapy minimally important
- Megesterol acetate seems inferior to above agents
- Recent data suggests lack of prior endocrine response does not predict lack of response to additional endocrine agent.
FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENCE/STAGE IV DISEASE

Continue endocrine therapy until progression or unacceptable toxicity → Progression → No clinical benefit after 3 consecutive endocrine therapy regimens or Symptomatic visceral disease

Yes → Chemotherapy

No → Trial of new endocrine therapy
Crossover to receive trastuzumab was actively offered to all patients who progressed on anastrozole alone

One patient did not receive study drug and was excluded from analyses

MBC, metastatic breast cancer

McKay et al, SABCS 2006
Progression-free survival

<table>
<thead>
<tr>
<th>Events</th>
<th>Median PFS</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>4.8 months</td>
<td>3.7, 7.0</td>
<td>0.0016</td>
</tr>
<tr>
<td>99</td>
<td>2.4 months</td>
<td>2.0, 4.6</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk
- A+H: 103 48 31 17 14 13 11 9 4 1 1 1 0 0 0
- A: 104 36 22 9 5 4 2 1 0 0 0 0 0 0

CI, confidence interval
PFS = time from randomisation to date of progressive disease or death

McKay et al, SABCS 2006
Patients with measurable disease evaluable for response

<table>
<thead>
<tr>
<th></th>
<th>A+H (n=74)</th>
<th>A (n=73)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>20.3</td>
<td>6.8</td>
<td>0.018</td>
</tr>
<tr>
<td>Stable disease (&gt;6 months)</td>
<td>37.8</td>
<td>38.4</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>40.5</td>
<td>49.3</td>
<td></td>
</tr>
</tbody>
</table>

McKay et al, SABCS 2006
Overall survival

Events | Median OS | 95% CI | p value
---|---|---|---
58 | 28.5 months | 22.8, 42.4 | 0.325
64 | 23.9 months | 18.2, 37.4

No. at risk

- A+H: 103, 91, 83, 76, 63, 49, 36, 24, 12, 4, 3, 0, 0
- A: 104, 96, 87, 73, 58, 42, 34, 22, 5, 2, 1, 1, 0

73 / 104 patients (70%) received H later during the course of disease

McKay et al, SABCS 2006
Hormonal Therapy of Metastatic Breast Cancer

- Effective only in those with ER and/or PR positive breast cancer
- High rates of response
- Sequential responses common
- Longer durations of response than with chemotherapy
- Less toxicity compared with cytotoxics
- Response rates across hormonal therapies similar
- Major criteria for preference is toxicity
SUBSEQUENT HORMONAL THERAPY FOR SYSTEMIC DISEASE  
(For first-line hormonal therapy see BINV-16)

Premenopausal patients with ER-positive disease should have ovarian ablation/suppression and follow postmenopausal guideline

POSTMENOPAUSAL PATIENTS
- Non-steroidal aromatase inhibitor (anastrozole, letrozole) or steroidal aromatase inactivator ( exemestane)
- Fulvestrant
- Tamoxifen or Toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol
TREATMENT OF RECURRENCE/STAGE IV DISEASE

Systemic disease

Bone disease present → Add bisphosphonate

ER and/or PR positive; HER2 negative

ER and/or PR positive; HER2 positive

ER and PR negative, or ER and/or PR positive and endocrine refractory; HER2 negative

ER/PR negative; HER2 positive

Bone disease not present

See BINV-17

See BINV-18

See BINV-19

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TREATMENT OF RECURRENT/STAGE IV DISEASE

ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE

- Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women
- Consider initial chemotherapy

ER and/or PR positive; HER2 negative
- Premenopausal
- Postmenopausal
- Visceral crisis

ER and/or PR positive; HER2 positive
- Premenopausal
- Postmenopausal
- Visceral crisis

No prior endocrine therapy within 1y
- Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women or Anti estrogen
- Aromatase inhibitor or Anti estrogen

Prior endocrine therapy within 1y
- Consider initial chemotherapy