Preoperative Hormonal Therapy

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Professor of Cancer Medicine
Royal Marsden Hospital, London
NCI Conference Washington
27th March 2007
Estrogens Before Surgery for Large Breast Cancers

“The cancers in the treated patients were altered by complete or partial softening. Many of the tumours became mobile, smaller and more difficult or impossible to palpate....”.

Kennedy et al Cancer Sept 1957
How Effective Is Preoperative Hormonal Therapy in:

1. Achieving Clinical Tumour Regressions?

2. Downstaging to Avoid Mastectomy?
Randomised Preoperative Hormonal Therapy Trials

B-24  Tamoxifen  v  Letrozole
IMPACT  Tamoxifen  v  Anastrozole  v  Combination
PROACT  Tamoxifen  v  Anastrozole  (+CT)
0223  Anastrozole  v  Anastrozole  +  Gefitinib
        Tamoxifen  v  Exemestane
        Anastrozole  v  Exemestane  v  CT

First 4 double blind, multicentre, postmenopausal, ER and/or PgR+ve
P24: Preoperative Tamoxifen v Letrozole

• 337 patients  Median age 68
• 4 months treatment
• None suitable for conservative surgery
• 14% locally advanced
• Primary endpoint: Clinical Objective Response

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen</th>
<th>Letrozole</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>170</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical OR</strong>*</td>
<td>36 (4)%</td>
<td>56 (10)%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ultrasound OR</strong>*</td>
<td>25%</td>
<td>35%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>BCS</strong></td>
<td>35%</td>
<td>45%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Overall Response  **Breast Conserving Surgery*  
IMPACT: Preoperative
Tamoxifen v Anastrozole v Combination

- 330 patients Median age 73
- Median tumour diameter 3.8 (1-15) cm
- 3 months treatment
- 96 (44%) suitable for conservative surgery
- No locally advanced
- Primary endpoint: Clinical Objective Response

Smith et al  JCO 23: 5108  2005
**IMPACT: Preoperative Tamoxifen v Anastrozole v Combination**

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen</th>
<th>Anastrozole</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>108</td>
<td>113</td>
<td>109</td>
</tr>
<tr>
<td>Clinical OR*</td>
<td>36%</td>
<td>37%</td>
<td>39%</td>
</tr>
<tr>
<td>Ultrasound OR*</td>
<td>20%</td>
<td>24%</td>
<td>28%</td>
</tr>
<tr>
<td>BCS**</td>
<td>22%</td>
<td>46%</td>
<td>26%</td>
</tr>
</tbody>
</table>

* Overall Response  **Breast Conserving Surgery

Smith et al. JCO 23: 5108 2005
PROACT: Preoperative Tamoxifen v Anastrozole

- 451 patients + Chemotherapy
- 330 no CT
- 3 months treatment
- >3cm operable or locally advanced
- Primary endpoint: Clinical Objective Response

Cataliotti et al Cancer 106: 2095; 2006
# PROACT: Preoperative Tamoxifen v Anastrozole (Endocrine Therapy only)

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen</th>
<th>Anastrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>151</td>
<td>163</td>
</tr>
<tr>
<td><strong>Clinical OR</strong>*</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Ultrasound OR</strong>*</td>
<td>27%</td>
<td>36%</td>
</tr>
<tr>
<td><strong>BCS</strong></td>
<td>31%</td>
<td>43%</td>
</tr>
</tbody>
</table>

* Overall Response  **Breast Conserving Surgery

Cataliotti et al Cancer 2006
## Preoperative Exemestane vs Tamoxifen

151 patients

<table>
<thead>
<tr>
<th></th>
<th>Clinical ORR (%)</th>
<th>Ultrasound ORR (%)</th>
<th>BCS Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exemestane (n=76)</td>
<td>76.3</td>
<td>60.5</td>
<td>36.8</td>
</tr>
<tr>
<td>Tamoxifen (n=75)</td>
<td>40.0</td>
<td>37.3</td>
<td>20.0</td>
</tr>
<tr>
<td><em>P Value</em></td>
<td>&lt;0.05</td>
<td>0.092</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

ACOSOG Z1031: Randomized Neoadjuvant AI Protocol

ER+ PMW Stage II and III Target: 375 pts

4 months

Surgery

Postsurgery management at investigator’s discretion

ACOSOG = American College of Surgeons Oncology Group.
Is Preoperative Endocrine Therapy As Effective As Chemotherapy?
### Preoperative Exemestane v Anastrozole v CT

<table>
<thead>
<tr>
<th></th>
<th>Exemestane</th>
<th>Anastrozole</th>
<th>Adria/ Taxol</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>80%</td>
<td>91%</td>
<td>38%</td>
</tr>
<tr>
<td>BCS</td>
<td>33%</td>
<td>38%</td>
<td>21%</td>
</tr>
</tbody>
</table>

117 older patients ER+ve

Randomise

Semiglazov SABCC. 2004
What Is the Optimal Duration of Preoperative Endocrine Therapy?

AI Response Rates %

2 consecutive trials run by same investigators with similar entry criteria

Response %

<table>
<thead>
<tr>
<th></th>
<th>P24</th>
<th>IMPACT</th>
<th>223</th>
</tr>
</thead>
<tbody>
<tr>
<td>4mo</td>
<td>56</td>
<td>37</td>
<td>61</td>
</tr>
<tr>
<td>3mo</td>
<td>56</td>
<td>37</td>
<td>61</td>
</tr>
<tr>
<td>4mo</td>
<td>56</td>
<td>37</td>
<td>61</td>
</tr>
</tbody>
</table>

Letrozole  Anastrozole
Tamoxifen Alone v Surgery + Tamoxifen: ‘Golden Oldies’

- CRC UK trial tamoxifen alone v surgery and tamoxifen
- 451 women 70 years or over
- significantly higher loco-regional relapse rate with tamoxifen alone [23% v 8%]
- Overall and breast cancer mortality worse (HR 1.68) although curves did not diverge for 3 years

Fennessy et al Br J Surg 91:699 2004
63 patients on Letrozole > 3 months
Changes in Clinical Volume over Time

Mean, Median and 95% CI of Mean

Dixon et al Edinburgh Breast Unit
63 patients on Letrozole > 3 months:
Time to Treatment Failure

Dixon et al Edinburgh Breast Unit
Duration of Neoadjuvant AI Therapy: Conclusions

• Continuing Response for up to 2 years in some patients
• Longer duration may increase breast conservation
• Optimum duration not yet clear
• In general, not a long term substitute for surgery
Which Patients Are Most Likely to Respond to Preoperative Endocrine Therapy?
Neoadjuvant Letrozole vs Tamoxifen (P024): Response by ER Expression

% of cases in each category

% Respon

ER Allred score

Logistic regression analysis of linear model

*Only 18 patients had ER scores of 3-5.
IMPACT (Anastrozole, Tamoxifen and Combination) Clinical Response Rate by ER Quartiles

Overall correlation p=0.02

IMPACT (Anastrozole, Tamoxifen and Combination)
Clinical Response Rate by ER Quartiles

Overall correlation p=0.02

Clinical Response (%) in HER2+ Tumours

Letrozole: P024
227 pts

L T
15/17 4/19

Response rate (%)
21% 88%
P = 0.0004

IMPACT
239 pts

A T
7/12 2/9

Response rate (%)
58% 22%
P = 0.09


Smith et al. JCO 23: 5108 2005
Letrozole v tamoxifen by HER2 status
DFS (BIG 1-98 Central Analysis)

- All patients (n=4399) - Hazard Ratio (L:T) = 0.71
- ER+ / HER2- (n=3971) - Hazard Ratio (L:T) = 0.72
- ER+ / HER2+ (n=234) - Hazard Ratio (L:T) = 0.68

Favors L

Favors T

Viale et al SABCC.2005
**Anastrozole vs tamoxifen by HER2 status: DFS**

(TransATAC central analysis)

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Events</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2-</strong></td>
<td>1526</td>
<td>149</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>HER2+</strong></td>
<td>190</td>
<td>45</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td>1786</td>
<td>200</td>
<td>0.72</td>
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</table>

**HR (A:T) and 95% CI**

- Anastrozole (A) better
- Tamoxifen (T) better

Dowsett et al SABCC.2006
Can Neoadjuvant Endocrine Therapy Provide Short Term Surrogate Endpoints for Long Term Outcome?
Can Neoadjuvant Endocrine Therapy Provide Short Term Surrogate Endpoints for Long Term Outcome?

- Clinical Objective Response?

<table>
<thead>
<tr>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
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<tbody>
<tr>
<td>P24 Letrozole v Tam</td>
<td>BIG 1-98</td>
</tr>
<tr>
<td>IMPACT A v T v C</td>
<td>ATAC</td>
</tr>
<tr>
<td>PROACT A v Tam</td>
<td>ATAC</td>
</tr>
<tr>
<td>HER2+ve P24/ IMPACT</td>
<td>ATAC/B 1-98</td>
</tr>
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Yes

No
Can Neoadjuvant Endocrine Therapy Provide Short Term Surrogate Endpoints for Long Term Outcome?

- Path Complete Remission?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Group 1</th>
<th>Group 2</th>
<th>pCR</th>
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<tbody>
<tr>
<td>IMPACT</td>
<td>A v T v C</td>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td>223</td>
<td>A v A +G</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>P24</td>
<td>L v T</td>
<td></td>
<td>1.5%</td>
</tr>
</tbody>
</table>
Can Neoadjuvant Endocrine Therapy Provide Short Term SurrogateEndpoints for Long Term Outcome?

• Molecular Endpoints?
IMPACT: Ki67 % Change (95% CI) from Baseline* During Treatment

Weeks

0 2 12

Ki67

A v T p=0.004

A v T p<0.001

* Via transformation of geometric mean proportion of baseline

Dowsett and Smith Clin Cancer Res 2005; 11: 951s-958s
IMPACT Ki67 (%): individual patient plots — anastrozole

The graph shows the proliferation Ki67 (%) over time (weeks) for anastrozole treatment, categorizing patients into Poor Ki67 responders, Good Ki67 responders, and Short Ki67 responders.
223 Anastrozole ± Gefitinib Neoadjuvant Trial Design

206 pts
Randomise

Anastrozole
Molecular Response - 2wks
-Ki67
-mRNA
Clinical Response - 4 months
Surgery

Anastrozole
Gefitinib

4 mo
Mean change in Ki67: baseline to 16 wks

- Anastrozole
- V.
- Placebo
- Anastrozole
- Gefitinib

A + G (n=59)  A alone (n=50)
-77.4%  -83.6%

Change in Ki67 levels (%)

16 weeks

p=0.26

Dowsett, Smith et al  ASCO 2006
Objective tumour response rates

Initially sensitive and less sensitive (Ki67)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Initially sensitive (Ki67)</th>
<th>Initially less sensitive (Ki67)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anastrozole + gefitinib</td>
<td>Anastrozole alone</td>
</tr>
<tr>
<td>0</td>
<td>25/38</td>
<td>12/25</td>
</tr>
<tr>
<td>10</td>
<td>18/39</td>
<td>8/21</td>
</tr>
<tr>
<td>20</td>
<td>12/25</td>
<td>6/21</td>
</tr>
<tr>
<td>30</td>
<td>6/21</td>
<td>4/20</td>
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<tr>
<td>40</td>
<td>4/20</td>
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<tr>
<td>50</td>
<td>2/16</td>
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<tr>
<td>60</td>
<td>1/11</td>
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<td>1/11</td>
<td>1/11</td>
</tr>
<tr>
<td>90</td>
<td>1/11</td>
<td>1/11</td>
</tr>
<tr>
<td>100</td>
<td>1/11</td>
<td>1/11</td>
</tr>
</tbody>
</table>

Treatment difference: -19.6 (-41.4, 2.1); Treatment difference: -9.9 (-38.5, 18.6)
Can Short Term Molecular Endpoints With Neoadjuvant Endocrine Therapy Predict for Long Term Outcome *In the Individual Patient?*
IMPACT  RFS by Baseline Ln Ki67

Relapse Free Survival by Baseline LnKi67

Years since randomisation

Relapse Free Survival

<=2.25  N = 51  O = 5  E = 8.4
2.25-2.99  N = 55  O = 8  E = 9.9
3+  N = 52  O = 13 E = 7.7

Chis = 4.68  df = 1  p = 0.03
IMPACT RFS by 2 week Ln Ki67

Professor Dowsett to Discuss

Relapse Free Survival %

Years since Randomisation

<=0.8
N = 45  O = 3  E = 7.9

0.81-1.99
N = 60  O = 9  E = 10.6

2+
N = 54  O = 14  E = 7.4

χ² = 8.65  df = 1  p = 0.003

IMPACT 2005
UK POETIC Trial

Preoperative Endocrine Therapy

Individualising Care

- Postmenopausal.
- HR+ve

Endpoints

Standard Adjuvant Therapy

Ki67 molecular

DFS
Preoperative Endocrine Therapy: Conclusions (1)

- Aromatase inhibitors are more effective than tamoxifen

- Around 50% objective responses

- Breast conservation in >40% initially requiring mastectomy
Preoperative Endocrine Therapy: Conclusions (2)

- Optimum duration uncertain but at least 4 months
- Well worth thinking about instead of chemotherapy in older patients with strongly ER/PgR+ cancers
- How to select?
Preoperative Hormonal Therapy

Conclusions (3)

• Clinical response is not a reliable surrogate for long term outcome

• PathCRs are too rare to be a useful surrogate

• Molecular markers (including after short term therapy) are more likely to be useful as short term predictors of outcome