Lessons Learnt from Neoadjuvant Hormone Therapy

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10 Lessons Learnt from Neoadjuvant Endocrine Therapy
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Lesson 1

Neoadjuvant Endocrine Therapy is Effective at Shrinking Cancers and Saving Breasts
But it takes longer than Neoadjuvant Chemotherapy
But it takes longer than Neoadjuvant Chemotherapy
Lesson 2

The Efficacy of Neoadjuvant Endocrine Therapy is not widely appreciated
Neoadjuvant Endocrine Therapy

• Evidence of its efficacy has not spread

• Not widely used

• Neoadjuvant Chemotherapy in widespread use
Neoadjuvant Therapy:
Does everyone need Napalm?
Studies Comparing Neoadjuvant Chemo (CT) and Endocrine Therapy (ET)
Neoadjuvant Endocrine vs Chemotherapy

- 121 Postmenopausal women: Median age 68 years
- ER + large operable + LABC: Randomized
- CT - Adriamycin + paclitaxel 3 weekly x 4 OR
- ET - Anastrozole 1mg or Exemestane 25 mg – 3 months

Adverse Events

Chemotherapy  Aromatase Inhibitor

- Neutropenia
- Feb Neutropenia
- Infection
- Stomatitis
- Diarrhoea
- Neuropathy
- Alopecia
- Cardiotoxicity
- HotFlushes
- Fatigue
- Vaginal Bleeding
- Arthralgia
- Myalgia
Outcomes

*P = .054*
Don’t jump to Conclusions
Neoadjuvant CT vs ET

Alba et al J Clin Oncol 28:15s, 2010

- 95 patients, age 51 years (32-74), 54% premenopausal
- CT [EC-T] : HT [exemestane 25 mg daily x 24 weeks + goserelin in premenopausal pts]
- 66% RR for CT - 13% CR, 53% PR
- 48% RR for HT - 6% CR, 42% PR (p = 0.07)
- 3 pts with CT and 0 with HT achieved a pCR
- Mastectomy rate CT: 49%, HT: 35%; p = 0.18
Problems with Studies to date

- Alba included patients not currently treated by neoadjuvant endocrine therapy – usually postmenopausal women

- Compared suboptimal duration of endocrine therapy

- Similar problems with ongoing studies

- You would NOT use 3 months of adjuvant endocrine therapy so WHY would you use 3 months of neoadjuvant endocrine therapy????
How Effective is Neoadjuvant Chemotherapy in Postmenopausal Women?
OPERABLE BREAST CANCER
FNA or Core
Age, T, cN

OPERATION
Post AC x 4

Pre AC x 4
OPERATION

Seq tam for women ≥50 yrs. only

NSABP:B-18
B18 Updated DFS

N     Ev    HR    P
Post  496  292
Pre    487  255   .81  0.05
Overall Survival

Qualitative Treatment by Age Interaction

p=0.01

<50yrs

N Ev HR P
Post 388 167
Pre 381 139 .81 0.06

≥50yrs

N Ev HR P
Post 363 148
Pre 361 171 1.23 0.07
Lesson 3

Need to Target those most likely to benefit from Neoadjuvant Endocrine Therapy
O24: Response by ER Allred Category

% of cases in each category

Logistic regression analysis of linear model

Who is suitable for Neoadjuvant Endocrine Therapy?

- Postmenopausal women
- ER Rich Cancers (Allred 7+8)
- Older postmenopausal women but also
- Younger women with significant morbidities
Lesson 4

Agents of Choice for Neoadjuvant Endocrine Therapy: Aromatase Inhibitors
Meta-analysis of pre-operative aromatase inhibitor versus tamoxifen in postmenopausal woman with hormone receptor-positive breast cancer Jae Hong Seo et al Cancer Chemother Pharmacol (2009) 63:261–266
ACOSOG Z1031 Study Design
Cohort A

16 weeks

Postmenopausal ER+, Allred 6-8, clinical stage 2 and 3

Exemestane
Letrozole
Anastrozole

Continued AI therapy where possible.
Radiotherapy, chemotherapy discretionarly

# ACOSOG Z1031, Cohort A Clinical Responses

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>Treatment Arm</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EXE (n = 124)</td>
<td>LET (n = 127)</td>
<td>ANA (n = 123)</td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>25 (20%)</td>
<td>26 (21%)</td>
<td>20 (16%)</td>
<td></td>
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<tr>
<td>Partial Response</td>
<td>49 (40%)</td>
<td>66 (52%)</td>
<td>63 (51%)</td>
<td></td>
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<tr>
<td>Progression</td>
<td>8 (7%)</td>
<td>6 (5%)</td>
<td>9 (7%)</td>
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<tr>
<td>Clinical Response rate</td>
<td>74/124 (60%)</td>
<td>92/127 (72%)</td>
<td>83/123 (68%)</td>
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</tr>
</tbody>
</table>

Lesson 5

Optimal Duration of Neoadjuvant Endocrine Therapy NOT same as Duration of Neoadjuvant Chemotherapy
Patient at Presentation
Following 3 Months Letrozole
After 9 months of Letrozole
3 Years Later
Patient at Presentation
Patient at Presentation
Patient after 9 months AI
Same Patient after Radiotherapy
Cancer at Diagnosis
After 1 year of Letrozole
After 2 years of Letrozole
After Excision
After Radiotherapy
Final Result after Radiotherapy
After Debridement + Maggots
After 6 weeks Letrozole
After 3 months Letrozole
After 6 months Letrozole
After 2 years Letrozole
Edinburgh Duration Study

340 patients: Neoadjuvant Letrozole

- 39% eligible for BCS @ 3 months
- 53% eligible for BCS @ 6 months
- 67% eligible for BCS @ 9-12 months
- 78% became eligible by 2 years

- Longer durations of therapy increase BCS rate
- Optimal duration of neoadjuvant letrozole 9-10 months
Complete Pathology Response not so important to long term outcome in ER Positive Cancers?
ER vs Response to Neoadjuvant Chemotherapy

Guarneri et al JCO 2006: 24; 1037-44

- 1731 patients neoadjuvant chemotherapy
- 1163 ER positive: 556 ER Negative

Path CR Rate
- 24% for ER negative cancers
- 8% for ER positive cancers

p <0.001
Oestrogen receptor status, pathological complete response and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer

A E Ring, I E Smith, S Ashley, L G Fulford, and S R Lakhani


- 435 patients treated with neoadjuvant chemotherapy
Overall Survival related to Path CR

![Overall survival curve](image)

- Path CR (52)
- Not CR (383)

P = 0.02

Disease Free Survival in Patients with ER –ve and +ve Cancers vs Path CR

ER Negative

*Path CR (24)*

*Not CR (87)*

*P = 0.001*

ER Positive

*Path CR (22)*

*Not CR (249)*

*P = 1.0*
So when people ask me if I worry about the lower rate of Complete path CRs after Neoadjuvant Endocrine Therapy
Lesson 7

Histology Changes with Neoadjuvant Endocrine Therapy differ from those with Neoadjuvant Chemotherapy
Response to Letrozole

6 Weeks

3 Months

6 Months
Central scarring seen in 60% with letrozole vs 4% with Chemotherapy

\[ p < 0.0001 \]

Correlates with clinical response \( (p = 0.03) \)
Histological Patterns following Neoadjuvant Therapy

- **Diffuse**
  - 6% vs 18% p<0.05

- **Nodular**
  - 13% vs 20% NS

- **Scattered**
  - 21% vs 40% p=0.035

- **Path CR**
  - 2% vs 18% p=0.006
Are Complete Excision Rates after BCS following Neoadjuvant Endocrine Therapy and Neoadjuvant Chemotherapy the same?
Edinburgh Study

302 patients having BCS after Neoadjuvant Rx
- 203 Neoadjuvant Endocrine Tx
- 99 Neoadjuvant Chemotherapy

Rate of Successful BCS
- 189/203 (93%) after Neoadjuvant Endocrine therapy
- 74/99 (74%) after Neoadjuvant Chemotherapy
  • p<0.0001
Recent Visit to Edinburgh
Lesson 8

Neoadjuvant Endocrine Therapy works in Inflammatory and Invasive Lobular Breast Cancers
Inflammatory Cancer: Response to Letrozole
At Diagnosis
After 3 months Letrozole
After 6 months of Letrozole
Invasive Lobular Carcinomas Treated by Neoadjuvant Letrozole in EBU

- 63 invasive lobular cancers treated with Letrozole
- Mean Age 74.68 yr  Range 51 – 91yr
- Allred score 8=49, 7=10, 6=2, 5=2
- Operable 2-4cm n= 10, >4cm n=33
- Locally advanced n=20
- Response assessed at 3 months – Single observer
Mammographic Response in Invasive Lobular Cancer

At Diagnosis

After 3 months Letrozole
Response in HER2 Positive Invasive Lobular Cancer
Clinical Responses in Invasive Lobular Cancers at 3 months

% Reduction in Clinical Tumour Volume

- 100%
- 75-99%
- 50-74%
- 25-49%
- 0-25%
- Increase
Lesson 9

Long Term Local Control Rates following BCS after Neoadjuvant Endocrine Therapy Excellent
BCS after Neoadjuvant Letrozole

- 242 patients: BCS after ≥ 3 months letrozole
- Median age 76 years (range 51 to 93)
- 75% (182/242) had postoperative XRT
- Median follow up 3.64 years (range 0.39 to 13.50)

- Recurrence Free Local Survival
  - 97% @ 2 years
  - 95% @ 5 years
Local Recurrence related to XRT

![Graph showing local recurrence related to XRT treatment. The graph plots the probability of being disease free against time to local recurrence or last follow up in years. The graph indicates a statistically significant difference (p = 0.01) between the no radiation therapy (No RT) and radiation therapy (RT) groups.]
Lesson 10

Can Combine Neoadjuvant Endocrine Therapy with Oncoplastic Surgery to further increase Numbers suitable for BCS
38 patients aged from 53-85

- 28 Unifocal, 10 Mulifocal/Multicentric Cancers
Neoadjuvant Endocrine Therapy with Bilateral Therapeutic Mammaplasty in Edinburgh

38 patients aged from 53-85

- 28 Unifocal, 10 Multifocal/Multicentric Cancers

- 37 Complete Excision at 1\textsuperscript{st} operation

- 1 Re excision – No residual disease

- 2 minor wound problems

- NO local recurrences as yet
Edinburgh Approach in Mammaplasty Patients

- Simultaneous bilateral procedures
- Patient has to want smaller breasts
Ensure you know before you start what is important to the patient

Different things are important to different people
Edinburgh Approach in Mammaplasty Patients

- Simultaneous bilateral procedures
- Patient has to want smaller breasts
- Breast Surgeon + Plastic Surgeon
- Optimal reduction on ‘normal side’
- Make cancer breast match optimal reduction
- Single or multiple cancers
Central Cancer
Neoadjuvant Letrozole for 9 months
Bilateral Therapeutic Mammaplasty
Cancer Behind Right Nipple at Diagnosis
Cancer Post 8 months Letrozole
Central Cancer
WLE +
Bilateral
Therapeutic
Mammaplasty
Result after Surgery
So should everybody who will benefit from Neoadjuvant Therapy have Neoadjuvant Chemotherapy?
Lessons Learnt

• Neoadjuvant Endocrine therapy
  – Is effective at shrinking Cancers
  – Increases number of women who can save their breasts
  – Associated with low rate of local recurrence after BCS + XRT
  – Can be combined with Oncoplastic Surgery
What you are looking for may be in front of your Eyes
Neoadjuvant Letrozole: Is it time to try it

TRY OUR COUGH SYRUP
YOU WILL NEVER GET ANY BETTER
Use Your Head
Use more Neoadjuvant Endocrine Therapy
The End