Preoperative Endocrine Therapy: Appropriate Candidates

Ian E. Smith
Royal Marsden Hospital and Institute of Cancer Research, London

New York, October 13th 2012

How Active is Neoadjuvant Medical Therapy?

Clinical Response
 Chemotherapy: 75%
 Complete Remission: 30%
 Path CR: 10-50%
 Endocrine: 40-50%
 Path CR: 1-2%

Doesn’t necessarily mean chemotherapy is better!

Is There a ‘Best’ Neoadjuvant Endocrine Therapy?

Letrozole v Tam

Anastrozole v Tam

P-24 Eiermann et al 2001 IMPACT and PROACT Smith et al 2004
Premenopausal Neoadjuvant Endocrine Therapy for 24 Weeks
Anastrozole + G* v Tamoxifen + G*

ORR (%)  
51%  

Why Use Pre-operative Systemic Therapy?

• To downstage to avoid mastectomy
• To prolong survival
• To predict outcome in adjuvant trials
• To identify short term molecular markers to predict long term outcome for individual patients

Neoadjuvant AI v Tamoxifen: Breast-Conserving Surgery (%)

L v T: \( p = 0.03 ^* \)
Letrozole

Anastrozole

Eiermann et al Ann Oncol 2001  
IMPACT Smith et al JCO 2005
Why Use Pre-operative Systemic Therapy?

- To downstage to avoid mastectomy
- To prolong survival
- To predict outcome in adjuvant trials
- To identify short term molecular markers to predict long term outcome for individual patients

Single-Injection Depot Progesterone Before Surgery in 976 Women With Operable Breast Cancer: A Randomized Controlled Trial

Overall Survival


HR 0.92 CI 0.69-1.21 p 0.53

HR 0.70 CI 0.49-0.99 p 0.04

Why Use Pre-operative Therapy?

- To downstage to avoid mastectomy
- To prolong survival
- To predict outcome in adjuvant trials
- To identify short term molecular markers to predict long term outcome for individual patients
Anastrozole v Tamoxifen v Combination
No Correlation between Clinical Response (IMPACT) and long term outcome (ATAC)

39%
36%
37%
40
50

ATAC (Adjuvant) IMPACT (Neoadj)

HR 95.2% CI P Value
ANA vs TAM 0.83 0.71-0.96 0.0129
Comb vs TAM 1.02 0.88-1.18 0.7718

Phase 2 Neo-adjuvant Letrozole +/- Everolimus (RAD001) Breast Cancer Study

Clinical Response

Ki67 Suppression

BOLERO-2 Phase 3 After an AI: Exemestane + Everolimus PFS

EVE + EXE: 10.6 Months PBO + EXE: 4.1 Months


* Via transformation of geometric mean proportion of baseline
Preoperative Endocrine Therapy: Appropriate Candidates

How do we select who is appropriate?

‘Classical’ Neoadjuvant Endocrine Therapy

Several months

• Older patients with large ER+ve HER2-ve cancers otherwise requiring mastectomy. But…
  • Takes several months
  • Only appropriate for patients with large cancers (a minority)
  • pCRs very rare. Clinical endpoints soft. So how do you know CT might not also be of benefit?
• Age not the only parameter to select endocrine therapy

Why Use Pre-operative Systemic Therapy?

• To downstage to avoid mastectomy
• To prolong survival
• To predict outcome in adjuvant trials
• To identify short term molecular markers to predict long term outcome for individual patients
IMPACT: 2 Week Effect of Anastrozole on Ki67 in Individual Patients

**Innate biology**
- Prognostic

**Biology of treatment sensitivity**
- Prognostic and Predictive

**RFS by Ki67 in IMPACT: Pre vs 2 Week**

2 weeks endocrine therapy

- Relapse Free Survival by baseline LnKi67
- Relapse Free Survival by 2 week LnKi67

**Not significant**
- Multivariate analysis

HR 2.01 p 0.002

Dowsett, Smith et al JNCI 2007
Could Short Term Pre-operative Endocrine Therapy with Molecular Markers to Predict Outcome in Individual Patients Be Feasible for Standard Practice?

2 weeks

Molecular Markers

Pre-Operative Endocrine Therapy: Individualising Care (POETIC)

4000pts Postmen. HR+ve

Endpoints

K67 Genes

Ki67 Genes

RFS

3600 pts so far accrued in >100 centres

Smith (CI), Robertson, Dowsett

PEPI (Preoperative Endocrine Prognostic Index)

Based on: pT, N, ER, Ki67 after 3-4 months treatment

Problem: 3 months to wait

Ellis et al J Natl Cancer Inst 2008;100: 1380 – 1388
Tumor Ki67 After 4 weeks of Neoadjuvant Endocrine Therapy for Early Identification of Non-responders

If High Ki67 after 4 weeks stop endocrine therapy and switch to chemotherapy

Ellis et al SABCC 2009

BOLERO-2 Phase 3 After an AI: Exemestane + Everolimus PFS

HR = 0.36, 95% CI (0.27, 0.47)
Logrank P Value: <0.0001
EVE + EXE: 10.6 Months
PBO + EXE: 4.1 Months

No. of Patients Still at Risk:

Everolimus 485 385 281 201 132 102 67 43 28 18 9 3 2 0
Placebo 239 168 94 55 33 20 11 11 6 3 3 1 0 0

Baselga et al ECCO/ESMO September 2011

• Primary hormone resistance (n = 54)
  - TAM: 3.9 mo.
  - TAM + RAD: 5.4 mo.
  - HR = 0.74 (0.42-1.3)

• Secondary hormone resistance (n = 56)
  - TAM: 5.0 mo.
  - TAM + RAD: 17.4 mo.
  - HR = 0.38 (0.21-0.71)

Bachelot et al GINECO ECCO Sept 2011
How Can We Predict Acquired Resistance When Planning Adjuvant Endocrine Therapy?


IMPACT Ki67 (%): Individual Patient Plots on Anastrozole

IMPACT Ki67 (%): Individual Patient Plots on Anastrozole

De Novo Resistance
**IMPACT Ki67 (%): Individual Patient Plots on Anastrozole**

- **Anastrozole**

15% Acquired Resistance

---

**IMPACT Ki67: Both De Novo and Acquired Resistance Do Badly**

- **Anastrozole**

---

**Could This Preoperative (POETIC) Model be Adapted to Predict Acquired Resistance?**

- **AI (Chemotherapy)**

---

Dowsett et al. JNCI 43: 120 2011
Conclusions (1)

‘Classical’ Neoadjuvant Endocrine Therapy Is Appropriate for:

- Several months
- Older postmenopausal patients with large strongly ER+ HER2-ve breast cancers otherwise requiring mastectomy
- Potentially many other women with ER+ HER2-ve cancers who do not need additional chemotherapy
  But how to select…?

Conclusions (2)

Short Term Preoperative to Define Who Is Appropriate

- Short term preoperative endocrine therapy could be used to define these, through post-treatment Ki67 and other markers
- Appropriate for most patients- not just a minority
- Truly individualised therapy, by taking into account the innate sensitivity to therapy of each cancer
- Can it be done as a standard of care?
  The UK POETIC trial is first attempt

Summary Slide

- Neoadjuvant endocrine therapy can downstage large ER-ve HER2-ve breast cancers sufficiently to avoid mastectomy in up to 50% of postmenopausal women.
- Neoadjuvant aromatase inhibitors appear more effective at this than tamoxifen.
- Short term preoperative endocrine therapy for around 2 weeks prior to surgery is feasible for both small and large cancers of this type, and changes in the proliferation factor Ki67 after treatment appear more accurate than pretreatment levels in predicting outcome.
- This approach may greatly help in making decisions about the need for additional adjuvant chemotherapy.
- Unlike with standard neoadjuvant therapy, this approach is appropriate for most patients- not just a minority with small cancers.
- It represents truly personalised medicine, by taking into account the innate sensitivity to endocrine therapy of each individual cancer.
- The UK POETIC trial is testing the feasibility of this hypothesis as a new standard of care in early ER+ve breast cancer, and so far almost 4,000 postmenopausal women have been entered.