Systemic Therapy in Locally Advanced Breast Cancer: Neoadjuvant Therapy

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Which Breast Cancer Patients are Candidates for Preoperative Therapy?
NCI Consensus Conference on Preoperative Therapy 2007

• Standard of care for locally advanced disease

• In operable disease, any patient who will require the therapy with certainty is a candidate
  – If therapy is in question (ie incomplete staging), surgery first is optimal

• Always reasonable in the setting of a clinical trial
Potential Advantages of Preoperative Therapy

• Improved surgical outcome by downstaging (proven)
  • Inoperable → operable
  • Mastectomy → breast conservation

• Exposes micrometastastic tumor cells to chemotherapy at an earlier time point (not proven to impact outcome in operable disease)

• Ability to observe in vivo response to therapy (uncertain clinical implications)

• In clinical trials, opportunity to assess surrogate endpoints (major advantage from translational research perspective)
Potential Disadvantages of Preoperative Therapy

• Loss of complete preop pathologic staging (tumor size, nodes) – **may be countered by response information gained**

• Necessity for full multidisciplinary approach to achieve optimal results
  – Surg onc, med onc, rad onc, breast imaging, pathology

• Appropriate standards for local therapy less well established in preoperative therapy setting (nodal evaluation, radiation)
Evaluation Prior to Preop Therapy
NCI Consensus Conference on Preoperative Therapy 2007

- **Pathologic assessment** with CORE BIOPSY (FNA not generally acceptable)
  - Fully assess tumor including grade, invasion
  - Adequate tissue for ER, PR, and HER2 testing
- **Breast imaging** to determine extent of disease
  - Mammography
  - U/S as appropriate
  - MRI may add, but remains controversial as standard procedure in all patients
- **Clip placement** except for rare cases (e.g. inflammatory breast cancer)
  - Useful for both surgical excision and pathologic examination (even if undergoing mastectomy)
- **Staging for distant disease is standard of care for locally advanced disease**
Preop Systemic Chemotherapy: Choosing a Regimen
NCI Consensus Conference on Preoperative Therapy 2007

• Optimal chemotherapy regimen
  – No inherent reason to believe that a regimen that works post-op will not work pre-op
  – *An acceptable adjuvant regimen is an acceptable preoperative regimen*
What Is the Optimal Measure of Response to Preoperative Therapy?
NCI Consensus Conference on Preoperative Therapy 2007

- **DFS and OS are always the clinically relevant endpoints!!**

- Pathologic CR is the best available surrogate in chemotherapy trials
  - Some effective therapies do not impact pCR rates (endocrine therapy)
  - May be true for other biologics

- pCR needs a uniform definition across trials
  - **Preferred definition:** absence of invasive cancer in both breast and lymph nodes
Pathologic Complete Response (pCR) rates to preoperative chemotherapy by tumor subtypes:

- **ER+**
  - Grade 1-2: 7
  - Grade 3: 16

- **HER2+**, **ER+**
  - No Trastuzumab: 18
  - Yes Trastuzumab: 30

- **HER2+**, **ER-**
  - No Trastuzumab: 31
  - Yes Trastuzumab: 50

- **TNBC**
  - 34
Preoperative setting as a pathway to drug approval

NeoSphere: Preoperative HER2 Antibody Combinations


Patients with operable or locally advanced HER2+ BC (N=417)

Pertuzumab FDA approved in neoadjuvant setting in 2013 based on this trial

TH docetaxel + trastuzumab

THP docetaxel + trastuzumab + pertuzumab

HP trastuzumab + pertuzumab

TP docetaxel + pertuzumab

FEC trastuzumab

docetaxel x 4 → FEC x 3 trastuzumab q3w cycles 5–17

TH pCR, %

46

29

17

24

pCR in breast

TH

THP

HP

TP
Preoperative trial of T-DM1 versus Trastuzumab in HER2+

ADAPT Trial: Preoperative T-DM1 Trial

Harbeck N et al, ASCO 2015 abstract #506

Patients with operable or locally advanced ER+/HER2+ Breast cancer (N=130)

- T-DM1 every 3 weeks x 4
- T-DM1 every 3 weeks x 4 + endocrine therapy
- Trastuzumab + endocrine therapy

Surgery

Standard chemotherapy recommended post-op
All receive one year of trastuzumab post-op

pCR, %

- T-DM1: 41
- T-DM1/ET: 41.5
- T/ET: 7
Should Residual Disease after Preoperative Chemotherapy Guide Further Treatment?
NCI Consensus Conference on Preoperative Therapy 2007

• Achieving pathologic CR predicts for better outcome, BUT…
  – Not all patients with pCR remain free of recurrence
  – pCR substantially more common in ER- than ER+
  – Not all patients who do not achieve pCR do poorly

• ER and HER-2 targeted therapies should be administered as indicated and can alter outcome

• No study has demonstrated additional value of treating with more chemotherapy after “standard” (anthracycline/taxane) preop chemotherapy