NeoAdjuvant Chemotherapy

What Are the Benefits for the Patient and for the Investigator

Daniel F. Hayes, M.D.
Anne F. Schott, M.D.
Conflicts of Interest

- Neither Drs. Hayes nor Schott has any financial conflicts related to this presentation
  
  BUT

- Dr. Hayes may have some conflict from the audience after this presentation
  
  • To be settled over a nice wine, I hope!

AND

- If you heard Dr. Hudis yesterday, much of this will sound familiar!
What Are the Benefits of NACT?

- **Investigator:**
  - Publications
  - Promotions
  - Nice trips to wonderful cities in Italy!

- **BUT:** what about the PATIENT?
Neo-Adjuvant Chemotherapy (NACT)

Potential Reasons to Give NACT COMPARED to Classic, POST-adjuvant Chemotherapy:

- Improve Survival
- Facilitate Surgical Approach
- Monitor Response to Adjust Regimen
- Drug or Tumor Biomarker Discovery
Neo-Adjuvant Chemotherapy (NACT)

- Potential Reasons to Give NACT COMPARED to Classic, POST-adjuvant Chemotherapy:
  - *Improve Survival – Hypothetical Reasons:*
    - Earlier treatment (by a few weeks)
    - Pre-operative might have biological advantage
      - Avoid surgical disruption of tumor bed and micro-metastases seeding
      - Treat existing micro-metastases before growth factor storm caused by surgery

*Gunduz, N, Fisher B, Saffer E; Cancer Res 39:3861, 1979*
Benefits of Adjuvant Chemotherapy vs. NO Chemotherapy

Does NACT Reduce Mortality Compared to Post-Operative ACT?
NSABP B18 and B27: NACT Does NOT Improve Survival Compared to post-Op ACT

B18: AC Pre vs. Post Op

B27: AC Pre vs. AC-T Pre vs. AC Pre than T Post

Rastogi P et al. JCO 2008;26:778-785
Does NACT Reduce Mortality Compared to Post-Operative ACT?

NO!
Does NACT Facilitate Surgery Compared to Post-Operative ACT?

Inoperable Operable
Does NACT Facilitate Surgery Compared to Post-Operative ACT?
“Inoperability”
= “LOCALLY ADVANCED BREAST CANCER (LABC)”

• Five Grave Prognostic Findings of Haagensen:
  – Inflammatory
  – Peau d’orange
  – Skin nodules
  – Skin ulceration
  – Fixation to the Chest Wall

Haagensen, C.D. Clinical classification of the stage of advancement of breast carcinoma; Diseases of the Breast, 1986
NACT: LABC

Stage IIIb (T4):

It is difficult to find PRCTs, but overall body of literature suggests that LR recurrence is ~ 10-30% after NACT, Mastectomy, and Radiation.

IT IS NOT KNOWN IF THIS IS SUPERIOR TO POST-OP ACT

REGARDLESS, IT HAS BECOME THE STANDARD OF CARE AND I AGREE
Does NACT Facilitate Surgery Compared to Post-Operative ACT?

Operable

Inoperable
### NSABP B18: Breast Conservation Rates

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Lumpectomy Proposed (%)</th>
<th>LuLumpectomy Proposed (%)</th>
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<td>All Patients</td>
<td>66</td>
<td>65</td>
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<td>&lt;2.0 cm</td>
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*Fisher, et al., Journal of Clinical Oncology 15:2483-93, 1997*
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For patients with T3 Cancers, the rate of BCT went from 3% to 22% with NACT

Is There a Cost?

Does Breast Conserving Therapy After NACT Result in Higher in-Breast or Local-Regional Recurrence?
**NACT: Operable Breast Cancer**

- **NSABP B18:**
  - *Local-Regional Recurrence Rates*

<table>
<thead>
<tr>
<th>Treatment Failure</th>
<th>PostOp AC</th>
<th>NeoAdj AC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Num Pts</td>
<td>%</td>
<td>Num Pts</td>
</tr>
<tr>
<td>IBTR only</td>
<td>46</td>
<td>10</td>
<td>66</td>
</tr>
<tr>
<td>Local recurrence, except IBTR</td>
<td>23</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>35</td>
<td>5</td>
<td>29</td>
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### NACT: Operable Breast Cancer

- **NSABP B18:**
  - Local-Regional Recurrence Rates

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<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>Num Pts</td>
<td>112</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>12</td>
<td>3</td>
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IBTR HIGHER in Pre Op/NACT, but Not Statist Significant

*Rastogi, et al., J Clin Oncol 26:778-85, 2008*
Are there Subsets Who Do Not Benefit?

• **Patients who are already BCT Candidates**

• **Patients for whom a mastectomy will be done regardless of response**

• “Luminal A”: pCR ~10%
  – Houssami, et al EJC 2012
Does NACT Facilitate Surgery Operable

• Yes
  – Appropriate for patients with T3 lesions
  – Probably not appropriate for Luminal A

• If you are going to do this, give ALL the CTX BEFORE Surgery
Does NACT Permit In-Course Adjustments To Regimen?
Neo-Adjuvant Chemotherapy (NACT)

**In-course Adjustment to Regimen:**

**Hypothetical Justification:**

- Inactive therapy should not be given (for obvious reasons)
- Better therapy might be substituted
Neo-Adjuvant Chemotherapy (NACT)

- In-course Adjustment to Regimen

- Arguments Against:

  - Difficult to determine response: Clinical and radiographic measures are inaccurate

    - Schott, et al., Breast Cancer Res Treat 92:231-8, 2005

  - SEE Dr. several talks this AM

    - BUT: must be sure of analytical and clinical validities
Neo-Adjuvant Chemotherapy (NACT)

*In-course Adjustment to Regimen*

**Arguments Against:**

- Efforts to use other measures, like change in Ki67, are investigational
- And….they are fraught with technical difficulties between labs
  - Nielsen et al, *JNCI*, in press
Neo-Adjuvant Chemotherapy (NACT)

*In-course Adjustment to Regimen*

**Arguments Against:**

- Time to determine response is short, especially with Dose Dense Therapy:
  - AC = 8 weeks,
  - Paclitaxel or docetaxel = 8-12 weeks
Does NACT Permit Assessment of Prognosis and Indication for Additional Treatment After Standard Regimen?
Prognostic impact of pathologic complete response (pCR) on disease-free survival (DFS) in 4,193 patients according to breast cancer intrinsic subtype.

von Minckwitz G et al. JCO 2012;30:1796-1804
Neo-Adjuvant Chemotherapy (NACT)

- Prognosis and Additional Treatment

- Arguments Against:
  - pCR does NOT = 100% cure rate
  - Lack of pCR does NOT = lack of benefit
Prognostic impact of pathologic complete response (pCR) on disease-free survival (DFS) in 4,193 patients according to breast cancer intrinsic subtype.

von Minckwitz G et al. JCO 2012;30:1796-1804
Neo-Adjuvant Chemotherapy (NACT)

- Prognosis and Additional Treatment

- Arguments Against:
  - Is it possible that
    - Lack of pCR = intrinsic chemo Resistance?
      - Further Chemo will do no good??
    - pCR = not all are cured and they may be the ones with chemo sensitive cancers?
      - Perhaps these are the very patients who might benefit the most from further therapy????
Neo-Adjuvant Chemotherapy (NACT)

- Prognosis and Additional Treatment
  - No trials have demonstrated benefit of early change in regimen if patients are not having apparent response.
  - **Exceptions:**
    - GeparQuattro: cisplatin in Triple Negative Patients After Standard Ctx
    - B27: Docetaxel after AC = higher pCR
      - We already knew that addition of T after AC is superior. Does not help decide who should NOT get Taxane
Does NACT Permit Assessment of Prognosis

YES!!!

Indication for Additional Treatment

Insufficient Data

I would readily offer such a trial to a patient
Neo-Adjuvant Chemotherapy (NACT)

- Additional NON-Chemotherapy:
  - ER POS – Give endocrine therapy
  - HER2 POS – Optimal duration
    trastuzumab = 12 months (Pivot et al, SABCS 2012)

Both Given Regardless of pCR
Can NA Setting Be Used to Conduct Phase II Trials Compared to the Metastatic Setting?
**Neo-Adjuvant Chemotherapy (NACT)**

- Potential Reasons to conduct Phase II trials in the NA COMPARED to Classic Metastatic settings:
  - Metastatic disease may already be fundamentally resistant
    - EBCTG/success of adjuvant systemic therapy
    - Sequential heterogeneity
Tumour Phylogenetic Evolution
(Renal Cell Cancer)

Neo-Adjuvant Chemotherapy (NACT)

- Potential Reasons to conduct Phase II trials in the NA COMPARED to Classic Metastatic settings:

  - Determination of endpoint (response)
    - pCR may be easier to measure compared to clinical/radiographic determination of response
  - See Dr. Semiglazov
Is RECIST a Good Measure of Tumor Response?

Long Term Outcomes are More Robust Using Circulating Tumor Cell vs. Imaging Determination of Response

Budd, et al., Clin Cancer Res 12:6403-9, 2006
Clinical Trial Settings: Classic Strategy

Metastatic Setting

Phase I
N~ 30-50 pts

Phase II
N~ 50-200 pts

Phase III
N~ 200-500 pts

If Successful, Move to Adjuvant Setting
(total n treated ~ 700-1000)

Adjuvant Setting
Classic Phase III Adjuvant Trial (3-4000 pts)
Clinical Trial Settings: Neoadjuvant Strategy

Metastatic Setting

Phase I
N~ 30-50 pts

If Successful, Move to Adjuvant Setting
(totai n treated ~ 30-50)

Neo- Adjuvant Setting
Phase II (300-400 pts)
Neo-Adjuvant Chemotherapy (NACT)

- Concerns about conducting Phase II trials in the NA COMPARED to Classic Metastatic settings:
  - Different types of studies
    - Known Chemotherapies
      - eg. Cisplatin in Geparsixto
    - “Repurposed” drugs from other medical settings
      - eg. Metformin
    - Totally new drugs – Major Concern
**Neo-Adjuvant Chemotherapy (NACT)**

- Concerns about conducting Phase II trials in the NA COMPARED to Classic Metastatic settings:
  - Are there sufficient safety data for New Drug?
    - Prior phase I’s only detect major and common toxicities
    - If we bypass classic phase II and III trials in the metastatic setting, will we expose potentially curable patients to unexpected toxicities?
Neo-Adjuvant Chemotherapy (NACT)

- Concerns about conducting Phase II trials in the NA COMPARED to Classic Metastatic settings:
  - Are there sufficient data that New Drug will not antagonize chemotherapy?
    - Example: tamoxifen
Phase III SWOG 8814 (TBCI 0100)
Postmenopausal, N+, ER+

**RANDOMIZE**

- tamoxifen x 5 yrs
  - (n = 361)
- CAF x 6, with concurrent tam
  - (n = 550)
- CAF x 6, then tamoxifen
  - (n = 566)

**S8814: Overall Results**

Concurrent Tamoxifen and CAF is Inferior to Sequential CAF followed by Tamoxifen

Neoadjuvant Chemotherapy (NACT)

- Concerns about conducting Phase II trials in the NA COMPARED to Classic Metastatic settings:
  - Is pCR a good endpoint?
    - For chemotherapy: Yes
    - For endocrine therapy: No
    - For other investigational Therapy: ?
Neo-Adjuvant Chemotherapy (NACT)

- Concerns about conducting Phase II trials in the NA COMPARED to Classic Metastatic settings:

  - **Example: Tamoxifen**
    - **Toxicity:** *Probably would be OK*
    - **Safety:** *Concurrent therapy would antagonize Chemo*
    - **Efficacy:** *Would result in a false negative observation*
Can NA Setting Be Used to Conduct *Biomarker Studies* Compared to the Metastatic Setting?
Neo-Adjuvant Chemotherapy (NACT)

- Potential Reasons to conduct Biomarker Studies in the NA setting:
  - Serial Tissue Biopsy Feasible
    - Positive Examples:
      - NeoAdjuvant Endocrine Therapy
      - NeoAdjuvant Lapatinib
        - Li, et al., J Natl Cancer Inst 100:672-9, 2008
Effect of Neo-Adjuvant Chemotherapy and Lapatinib on Breast Cancer Stem Cells

Li, et al., J Natl Cancer Inst 100:672-9, 2008
Conclusions

- **NACT is clearly beneficial to facilitate surgery**
  - Locally advance Breast cancer
  - T3 patients who might become breast conservation candidates

- **NACT might be beneficial**
  - To change from futile therapy
  - To add additional therapy
  - To study potential benefits of unproven drugs
  - For predictive biomarker discovery
Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer
American Society of Clinical Oncology/College of American Pathologists
Clinical Practice Guideline Update
Wolff*, Hammond*, Hicks*, Dowsett*, McShane*, et al
simultaneously published in JCO and Archives of Path Lab Med
Oct 4, 2013

Thank You