After Preoperative Therapy: “What now?”

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Purposes of Preoperative Therapy

- Deliver effective systemic therapy
- Downstage tumor for surgery
- Assess dynamic response to therapy
  - Populations / research
    - Define efficacy of treatment regimen using surrogates for long-term outcomes
  - Individuals / clinical practice
    - Inform prognosis
    - Tailor treatment program based on response
Outline: After Preoperative Therapy

1. Surveillance
2. Systemic Therapy
Local-regional Recurrence after Preoperative Therapy

- The goal of preoperative therapy is surgical downstaging
- More patients are likely to have BCS after preoperative therapy
- Patients with BCS after preoperative therapy *may* be at higher risk for local-regional recurrence
- Local-regional recurrence constitutes a substantial percentage of breast cancer events in neoadjuvant patients, owing perhaps to higher stage at diagnosis
Neoadjuvant therapy compared with adjuvant therapy for breast cancer

Recurrences in NSABP B-27


A. LOCAL

B. IPSILATERAL

C. REGIONAL

D. DISTANT
Local-regional surveillance

• No unique guidelines exist for local-regional surveillance after preoperative therapy
• Because of risk of local-regional events, clinicians should offer standard surveillance with a low threshold to further evaluate changes
Systemic Therapy and Surveillance After Preoperative Therapy

- All patients should receive standard biological adjuvant therapy
  - anti-estrogen therapy for ER+ tumors
  - anti-HER2 therapy (i.e. trastuzumab) for HER2+ tumors
- Surveillance for recurrence according to standard recommendations (e.g. ASCO)
- Threshold for evaluation of symptoms affected by residual risk, which may be informed by results of preoperative therapy
Systemic Therapy After Preoperative Therapy

• Is there a role for additional chemotherapy in patients with residual cancer after neoadjuvant chemotherapy?
MDACC – Randomized Trial of Adjuvant Chemotherapy after Preoperative Chemotherapy

200 patients enrolled
  5 not eligible
  2 not evaluable

193 evaluable and received preoperative chemotherapy
  3 received radiation as their only local therapy
  1 received no local therapy

189 underwent surgery as primary local therapy
  8 received preoperative radiation

181 evaluable for response to preoperative chemotherapy

71 pathologic CR or ≤ 1cm³ residual disease
  1 refused further chemotherapy

70 received VACP

110 with >1cm³ residual disease
  4 not randomized

106 randomized

51 VACP
55 VbMF

Relapse-free survival by randomized treatment arm (dated from surgery)

Systemic Therapy After Preoperative Therapy

- In 2007, role for further chemotherapy is entirely unclear, and is a common clinical dilemma
  - Vast majority of patients will NOT have pCR, and are at greater risk of recurrence
  - Such patients have tumors that carry, by definition, some clinical resistance to chemotherapy
  - Many – if not all – patients will have had anthracycline-, alkylator- and taxane-based therapy (i.e. no standard “non-cross-resistant” options)
  - There are no data from the modern era to guide treatment recommendations for patients who have completed “standard” adjuvant chemotherapy regimen
  - In the absence of such data, additional chemotherapy should not routinely be administered
NSABP B-27 Disease-free Survival

Would more Rx be better?
Yes: tumor really sensitive to chemo
No: pt doing well already

Would more Rx be better?
Yes: high risk warrants therapy
No: tumor resistant already

The Post-Preoperative Patient: a high priority population for clinical research

- Substantial heterogeneity in clinical practice
- No standard consensus on best treatment approach following standard chemotherapy
- Higher risk of recurrence
- Relative resistance to established chemotherapy options
- Begins to deliver on the promise / premise of neoadjuvant therapy that treatment can be tailored based on dynamic response to therapy
The Post-Preoperative Patient: a high priority population for clinical research

Platform for Research Concepts

– Marker analyses for recurrence risk
  • Systemic
  • Local-regional

– Serial monitoring for early detection of recurrence
  • Systemic
  • In-breast

– Therapeutic intervention trials
  • “more therapy”
  • novel therapies
Surgery for Primary breast cancer within last 3 years
Stage ypT2-4 and / or ypN1-3, and M0
prior preoperative taxane-anthracycline containing chemotherapy

Observation

Stratification:
- Receptor status
- Time since surgery
- Age
- Center

Zoledronate 4 mg
- Every 4 weeks for the first 6 doses (year 0 to 0.5)
- Every 3 months for 8 doses (year 0.5 – 2.5)
- Every 6 months for 5 doses (year 2.5 – 5)

Prior and/or simultaneous standard endocrine/antiHer2 treatment
Prior and/or simultaneous radiotherapy
NaTaN - Recruitment at 01.01.2007
N = 206
Feasibility Study of Novel Therapies After Preoperative Chemotherapy

• Rationale: novel therapies needed for patient population with residual invasive cancer after preoperative chemotherapy
• Plan: sequential cohorts of 40 patients
• Endpoints: feasibility and safety of therapy
• Correlative studies: markers of angiogenesis activity, predictors of recurrence
# Pilot Feasibility Study of Novel Therapies After Preoperative Chemotherapy

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<th>Cohort 1</th>
<th>Bevacizumab</th>
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<td>Bevacizumab 15 mg/kg IV q 21 days x 1 year</td>
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<th>Cohort 2</th>
<th>Metronomic CM + bevacizumab</th>
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<tr>
<td></td>
<td>Cyclophosphamide 50 mg PO QD</td>
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<tr>
<td></td>
<td>Methotrexate 2.5 mg PO BID days 1,2 each week</td>
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<td>Bevacizumab 15 mg/kg IV q 21 days x 1 year</td>
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<tr>
<th>Cohort 3</th>
<th>Capecitabine + bevacizumab</th>
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<tr>
<td></td>
<td>Capecitabine 2000 mg/m² days 14 of 21 x 6 cycles</td>
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<tr>
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<td>Bevacizumab 15 mg/kg IV q 21 days x 1 year</td>
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Proposed Trial for Post Preoperative Therapy

Standard Neodjuvant Chemotherapy

Residual Invasive Breast Cancer

- anti-VEGF
- anti-VEGF & chemo
- chemo
Summary

- After preoperative therapy, patients receive standard radiotherapy, biologically-based adjuvant therapy, and surveillance.
- Patients who have completed preoperative therapy constitute an important population with unique and unmet oncological needs.
- Substantial opportunities exist to study patients after preoperative therapy to improve their cancer-related outcomes.