Early Stage Breast Cancer: Who needs adjuvant therapy?

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Overview

• Review of Breast Cancer Subtypes
• What is adjuvant therapy and why do we give it?
• Chemotherapy
  • Who benefits?
  • What are the options?
• Hormone therapy
  • What are the options, and how do they work?
    • Tamoxifen
    • Aromatase inhibitors
    • Ovarian suppression?
  • What is the optimal duration?
• Adjuvant Clinical trials
Subtypes and Targets

Hormone-receptor positive (ER+ and/or PR+)
- Anti-estrogens/“Hormone therapy”
- Chemotherapy

Her2-positive
- Anti-Her2 targeted therapy
- Chemotherapy

Receptor Negative (“Triple-negative”):
- Chemotherapy
- Looking for new “targets”
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What is adjuvant therapy?

• “Adjuvant” = postoperative therapy
  • +/- Chemotherapy
  • +/- Hormonal therapy
  • +/- Trastuzumab (Herceptin)
  • Radiation
How does cancer become “metastatic”

Circulating tumor cell “seeds” can travel to new sites and form tumors
Goal of Adjuvant Therapy

- Kill seed cells
- Prevent development of Stage IV disease
- Risk of seed cells vs side effect/benefit of therapy
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Who needs chemo?

• **Triple negative BC**: YES!
• **HER2 positive BC**: YES!

• **Hormone Positive Breast Cancer**: MUCH less clear!

• **Factors considered:**
  • Age and menopausal status
  • Other medical problems
  • Tumor size
  • Lymph node involvement
  • Oncotype DX recurrence score
What is the Onco
type DX™?

• Genetic test of breast tumor (usually removed at lumpectomy/mastectomy)
  • Assesses genes involved in invasion, cell growth, ER and HER2
• Validated for use in LYMPH NODE NEGATIVE, ER/PR+ breast cancer
• Reported as a “Recurrence Score” from 0 – 100
• Provides PROGNOSTIC and PREDICTIVE information
  • PROGNOSTIC: What is the risk of distant recurrence?
  • PREDICTIVE: What is the benefit of chemotherapy?
• Can help us determine which patients with ER/PR+ breast cancer benefit from chemotherapy
**Sample Oncotype DX™ Report: Page 1**

**Oncotype DX Breast Recurrence Score® Report**

**Node Negative**

<table>
<thead>
<tr>
<th>Recurrence Score® (RS) Result</th>
<th>Distant Recurrence Risk at 9 Years</th>
<th>Group Average Absolute Chemotherapy (CT) Benefit*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>17</strong></td>
<td><strong>5%</strong> (95% CI 4%, 6%)</td>
<td>RS 11-25 All Ages</td>
</tr>
</tbody>
</table>

**TAILORx**

Decisions on individual treatment especially around this RS 25 cutoff may consider other clinical factors.

Al: Antiestrogen inhibition / TAM: Tamoxifen
CI: Confidence interval

Exploratory Subgroup Analysis for TAILORx and NSABP B-20:

<table>
<thead>
<tr>
<th>Age</th>
<th>CT Benefit</th>
<th>RS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 years</td>
<td>No CT Benefit (&lt;1%)</td>
<td>&gt;15% CT Benefit</td>
</tr>
<tr>
<td>≤50 years</td>
<td>No CT Benefit (&lt;1%)</td>
<td>1.6% CT Benefit</td>
</tr>
</tbody>
</table>

Quantitative Single-Gene Scores

- **ER Positive**: 9.7 (47, 63, 178)
- **PR Positive**: 8.0 (3.9, 9.5, 25)
- **HER2 Negative**: 9.3 (1.8, 10.7, 18.0)
Chemotherapy Decision-making in ER+, LN- Breast Cancer

TAILORx Study:
• RS >26 → chemotherapy + endocrine therapy
• RS <15 → endocrine therapy only
• RS 15 – 25 → Age may matter

Age >50
• RS <26 → Endocrine therapy only

Age ≤ 50
• RS 21-25 → Strongly consider chemotherapy (benefit appears worth it in most cases)
• RS 16 – 20 → Consider chemotherapy (benefit even smaller)

Disclaimer: Every individual is different and factors such as tumor size, magnitude of ER/PR+, other health issues also play a role
Chemotherapy Decision-Making in ER+, LN+ Breast Cancer

• >3 lymph nodes ➔ chemotherapy beneficial for ALL

• 1-3 lymph nodes: more controversy
  • Pre-menopausal: Most likely benefit from chemotherapy (still standard)
  • Post-menopausal: *May* benefit from chemotherapy

Disclaimer: Every individual is different and factors such as tumor size, magnitude of ER/PR+, other health issues also play a role
Chemotherapy Options

• 1-3 chemotherapy drugs given every 1-3 weeks over the course of 3-6 months
  • Selection of regimen depends on tumor stage, receptor status, side effect profile

• Commonly used for adjuvant chemotherapy:
  • Adriamycin
  • Cyclophosphamide
  • Taxane (paclitaxel, docetaxel)
  • Carboplatin

• Anti-HER2 directed therapy incorporated ALWAYS if HER2+
  • Trastuzumab (Herceptin)
  • Pertuzumab (Perjeta)
What happens after chemotherapy?

- If you are a candidate for radiation → Radiation
- HER2-directed therapy will continue for a year (may overlap with radiation and endocrine therapy)
- Endocrine therapy follows chemotherapy + radiation
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How Hormone Therapies Work

Tamoxifen/SERM

Appropriate for pre- and post-menopausal women

Aromatase Inhibitor

Appropriate for post-menopausal women or pre-menopausal women with suppressed ovaries
Who Benefits from Endocrine Therapy?

- Anyone with ER and/or PR positive breast cancer
  - Reduces risk of breast cancer recurrence
  - Reduces risk of a second ER+ breast cancer
Tamoxifen: Candidates and Considerations

• Appropriate for women REGARDLESS of menopausal status
  • Slightly less effective than aromatase inhibitors so not preferred in post-menopausal women unless
    • Osteoporosis
    • Intolerance to AI’s
• Hot flashes, leg cramps, changes in periods
• Increased risk of blood clots
  • Similar to that seen with oral contraception/birth control
• Increased risk of endometrial cancer
  • Overall low risk (<2% risk over 5 years)
  • Must be evaluated if atypical bleeding
Aromatase Inhibitors (AI): Candidates and Considerations

- Must not have functioning ovaries
- Post-menopausal
- History of oophorectomy
- Medical ovarian suppression [monthly or every 3 month injections – leuprolide or goserelin]

- Increased risk of osteopenia/osteoporosis
  - Monitor bone density (DEXA)
  - Joint and muscle aches, stiffness
  - Hot flashes
Who benefits from Ovarian Suppression + AI?

- SOFT/TEXT
  - Pre-menopausal women who received chemotherapy derived a greater benefit from adding ovarian suppression to endocrine therapy (tamoxifen or AI)
  - Younger women (<35 years old) benefit the most

- Youngest, highest risk women

- BUT...long-term data is still limited
  - Weigh the benefits of improved breast cancer risk with quality of life and risks of “early menopause” (osteoporosis, cardiovascular disease)
What is the optimal duration of endocrine therapy?

• At a minimum – 5 years

• The decision to continue beyond 5 years depends on many things:
  • Prior therapy (what have you been taking the last 5 years)
  • Age and other health problems
  • Baseline recurrence risk
  • Side effects/tolerability of therapy
Extended Therapy Options

• 10 years tamoxifen
• 2-5 years of tamoxifen followed by 5 -10 years aromatase inhibitor
• 10 years of AI

• Absolute benefits of extended therapy increase the greater the risk of recurrence (more lymph nodes involved)
Endocrine Therapy Duration: Bottom Line

**Lowest risk**
- Lymph node negative
- Small tumors
- Low Oncotype


5 years probably sufficient

**Highest risk**
- Multiple positive LNs

Aim for 10 years

**Intermediate risk**
- 1-3+ lymph nodes
- Intermediate or high Oncotype

Need to weigh benefits with risk (quality of life, bone health)
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Adjuvant Therapy Clinical Trials

• Can any additional medications or interventions not currently approved help further reduce the risk of recurrence, or reduce the toxicity of treatment?

Examples:

• Adding targeted therapies to endocrine therapy (eg CDK4/6 inhibitors: palbociclib, ribociclib, abemaciclib)
  • PALLAS: Endocrine therapy + Palbociclib – completed, awaiting results

• Targeting “minimal residual disease” (MRD)
Conceptual Model of Recurrence During Surveillance

**Primary Cancer**  
Breast

**Minimal Residual Disease**  
Blood & Bone Marrow

**Recurrence**  
Metastatic Sites

"Seed cells" leave primary tumor  
Find sanctuary site, enter dormant state, stop dividing  
Awaken, reactivate, start dividing  
Travel to distant metastatic sites, begin multiplying
CLEVER Pilot Trial Design

- Patients screened via BM aspirate/ IHC for DTCs
  - Disclosure via phone
  - Education on test characteristics
- DTC+ enter CLEVER trial
  - Randomized, controlled, open label proof-of-concept
  - Oral, continuous daily dosing:
    - Hydroxychloroquine (HCQ)
    - Everolimus (EVE)
- Primary endpoint: feasibility
- Secondary: DTC-clearance
- 3-year recurrence-free survival

- Speak with a clinical trial navigator Monday-Friday, 9:00am to 5:00pm Toll Free: **1-855-216-0098**

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Summary

• Chemotherapy, radiation and endocrine therapy are incorporated in the adjuvant setting to prevent breast cancer recurrence

• Both breast cancer-specific and patient-specific factors are considered when determining an individual treatment plan
  • Chemotherapy or no? Which regimen? Type and duration of endocrine therapy

• With the improvements in adjuvant therapy, more breast cancer patients are becoming long-term survivors

• Studies are ongoing to increase the number of patients cured of breast cancer
Thank You!