Welcome to Master Class for Oncologists

Miami, FL
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Session 4:
3:30 PM - 4:15 PM

Adjuvant Endocrine Therapy: Therapeutic Choices and Factors Affecting Recurrence in Hormone Receptor-Positive Breast Cancer

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Presenter Disclosure Information

The following relationships exist related to this presentation:

• Dr Burstein has no relationships to disclose.

Off Label/Investigational Discussion
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Adjuvant Endocrine Therapy

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Deep time: risk of recurrence of ER+ tumors

EBCTG Overview
2000

Tamoxifen 5 yrs vs Not

RECURRENTS

Tam

Nil

ER+
Recurrence Risk Over Time for ER+ Cancers Treated with Adjuvant Endocrine Therapy (tam + OA)

Tamoxifen

Duration of Tamoxifen: NSABP B-14
Fisher, et al. JNCI 2001

Duration of Tamoxifen: NSABP B-14
Fisher, et al. JNCI 2001; median f/u 7 years post-rerandomization

ATLAS alone: ~10 vs ~5 years
Postmenopausal, ER+ Breast Cancer

Estrogen Levels in Women and Men


Aromatase Inhibitor Therapy

Stop AI

TAM

AI

TAM

AI

Plac

0
2
3
5
10
Years After Diagnosis

Recurrence

Cohort 1

5-yr gain 2.9% (SE 0.7)
8-yr gain 3.9% (SE 1.0)
Logrank 2P<0.00001

Tamoxifen

Recurrence rates (%/year) and logrank analyses

Years 0-1
Years 2-4
Years 5+

AI 1.69 (163/9647) 2.31 (261/11297) 2.33 (160/6879)
Tamoxifen 2.46 (234/9510) 2.81 (307/10938) 2.78 (180/6478)
Rate ratio, 0.67 SE 0.08 0.81 SE 0.08 0.83 SE 0.10
from (O-E)/V -38.4/96.6 -29.5/137.9 -15.7/83.0

Cohort 2

2-3 Yr Tamoxifen then 3-3 Yr (AI vs Tam)

ER+

Recurrence

Time since Treatments differ

3-yr gain 3.1% (SE 0.6)
6-yr gain 3.5% (SE 1.1)
Logrank 2P<0.00001

Tamoxifen

Recurrence rates (%/year) and logrank analyses

Years 0-1
Years 2-4
Years 3-5

AI 1.68 (187/11134) 2.81 (149/5298) 3.21 (23/716)
Tamoxifen 2.76 (303/10962) 3.00 (150/5007) 3.87 (27/697)
Rate ratio, 0.60 SE 0.07 0.93 SE 0.11 0.85 SE 0.27
from (O-E)/V -51.0/118.4 -5.5/72.6 -2.0/12.1

BIG 1-98 Sequential Therapy

2-Arm Option

A

TAM

B

Tamoxifen

4-Arm Option

A

Tamoxifen

N=1548*

B

Letrozole

N=1546

C

Tamoxifen

N=1548

D

Letrozole

N=1540

Enrolled

1999-2003

N= 6,182

*612 patients (39.5%) selectively crossed over to letrozole after the tamoxifen arm was unblinded. The present analysis includes only 3 blinded arms (B, C, D).

Is a sequence of agents superior to letrozole monotherapy?
Biomarkers and Selection of Therapy:
These are typically markers of risk, but not of treatment selection, for adjuvant endocrine therapy.
Genomic Health-NSABP B-14 Prospective Clinical Validation Study

- **Objective**
  - Validate Recurrence Score as predictor of distant recurrence in N-, ER+, Tamoxifen-treated patients
- **Design**
  - Randomized
  - Placebo–Not Eligible
  - Tamoxifen–Eligible
  - Registered
  - Pre-specified gene assay
  - Blinded laboratory analysis of three 10 micron tumor block sections

Predictive Factors: Sensitivity to Therapy

- **Key Factors**:
  - Subtype
  - ER expression
  - Recurrence score / signature
  - HER2, Ki-67, PR
  - Grade

ASCO Technology Assessment on Use of Aromatase Inhibitors: Status Report 2004

- Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone-receptor positive breast cancer should include an aromatase inhibitor. Neither the optimal timing nor duration of aromatase inhibitor therapy is established.
Individualized Adjuvant Endocrine Therapy in Postmenopausal Breast Cancer: Practical Suggestions

Lower risk:
Smaller T stage, node-negative, ER- and PR-positive, HER2-negative, low grade, low recurrence score, low Ki-67
Tam, AI, or Tam → AI

Higher risk:
Larger T stage, node-positive, ER/PR low, HER2-positive, higher grade, higher recurrence score, high Ki-67
Upfront AI

Risk Score Development

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Levels Examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>&lt; 55 v 55-69 v 70+</td>
</tr>
<tr>
<td>Involved nodes</td>
<td>0 v 1-3 v 4-9 v 10+</td>
</tr>
<tr>
<td>ER % stained</td>
<td>50+ v 30-49 v &lt; 30</td>
</tr>
<tr>
<td>PgR % stained</td>
<td>70+ v 20-69 v &lt; 20</td>
</tr>
<tr>
<td>Ki-67 LI %</td>
<td>&lt; 14 v 14-33 v 34+</td>
</tr>
<tr>
<td>HER2</td>
<td>Negative v positive</td>
</tr>
<tr>
<td>Peritumoral Vascular Invasion</td>
<td>Absent v present v unavailable</td>
</tr>
<tr>
<td>Pathological Grade</td>
<td>1 v 2 v 3</td>
</tr>
<tr>
<td>T size, cm</td>
<td>&lt; 2 v 2-4.9 v 5+</td>
</tr>
</tbody>
</table>

BIG 1-98: STEPP DFS by risk score

Side Effects of Adjuvant Therapy in Postmenopausal Women

Favors Tamoxifen
- Osteoporosis
- Bone fracture
- Arthralgia / myalgia
- Sexual function

Favors AI
- Genitourinary bleeding
- Endometrial cancer
- Venous thromboembolism

More or less the same
- Hot flashes / night sweats
- Headache / dizziness
- GI side effects
- Compliance

Could CYP2D6 account for differences between AIs and tamoxifen?

Tamoxifen Metabolic Pathway

CYP2D6 Genotype and Endoxifen

- *P < 0.001, r^2 = 0.24*

Graph showing Plasma Endoxifen (nM) for Wt/Wt, Wt/*4, and *4/*4 genotypes with CYP2D6 Genotype.

Heterozygous (wt/*4)

Graph showing Kaplan-Meier Estimates of Time to Recurrence, Event-Free Survival, and Disease-Free Survival for heterozygous patients.

Model results for disease-free survival in the unselected population and in each genotypic subgroup.

Kaplan-Meier Estimates of Recurrence Probabilities Comparing Tamoxifen With a Hypothetical AI Curve

- Hypothetical AI
- Unstratified
- EM
- EM 95% CI
- Decreased

Graph showing Kaplan-Meier Estimates of Recurrence Probabilities with follow-up years.

NCCTG 89-30-52

- 5 years tamoxifen (n = 256)
- 5 years tamoxifen + 1 year fluoxymesterone (n = 285)

Postmenopausal women
Early ER+ breast cancer

541 women accrued

Current state of CYP2D6 testing

- Multiple alleles (> 40) with varying degrees of metabolic efficiency
- Extensive ethnic variation
- Correlation between genotype: endoxifen: outcome is certainly not 1:1:1
- No data on prospective testing and treatment decision making as yet
- Testing not yet ready for primetime

Premenopausal ER+ Breast Cancer

The real question:
What to do about ovarian function?

Why do we still await answers?

- Historical artifact
  - 1990 overview / tamoxifen in premenopausal women
  - Trials of OFS ± tamoxifen vs chemotherapy
  - Don’t ask the key question of tam +/- OFS
- Confounder
  - Chemotherapy-induced amenorrhea

Data principally from ZIPP trial
- Most women in 40s
- 40%+ received chemo
IBCSG Trial 13-93
A[EJC] → CMF ± tamoxifen for premenopausal node-positive breast cancer

1. Amenorrhea → better outcome
2. Amenorrhea effect seen with or without tamoxifen and thus likely to be additive to tamoxifen benefit

Confounded by:
Age: median 43 years
ER status: 18% negative, 42% unknown
Chemotherapy administration: 80%
Noncompliance with OFS: 12%

Subgroup analysis of overall survival by chemotherapy and age among patients in the Adjuvant Breast Cancer Ovarian Ablation or Suppression (OAS) Trial

Trial Design ABCSG-12
- Accrual 1999-2006
- 1,803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years
- Surgery (HR) → Goserelin 3.6mg q28d → Randomize 1:1:1:1

Target sample size: 3000 patients

* Randomization within a 6-month evaluation period after end of CT, or within 12 weeks after definitive surgery for patients with no CT CT=chemotherapy, T=tamoxifen, E=exemestane, OFS=ovarian function suppression using triptorelin x 5 years or surgical oophorectomy or ovarian irradiation
Case Series

Smith, et al. JCO 2006
- 45 women in 40s with CRA on AI therapy
- 12 (27%) recovered OF
- 8 of the 12 had ↓ FSH, LH
- Median time to recovery of OF: 12 m (4 to 59 m)
- Median duration of AI therapy: 6 m

Burstein, et al. CBC 2006
- 8 women in 40s with CRA who began AI therapy, all of whom recovered OF
- FSH, LH single time-point measurements not predictive of recovery of OF

Premenopausal Patients: Clinical Summary

- Tamoxifen is the standard recommendation
- Consider OFS + tamoxifen in women with:
  - Lower risk tumors not receiving chemotherapy
  - Higher risk tumors but not experiencing amenorrhea with chemotherapy
- Trade-offs: greater toxicity
  - Menopausal symptoms, weight gain, musculoskeletal symptoms, sexual dysfunction, osteoporosis

Questions & Answers

Thank you for attending Master Class for Oncologists