Inflammatory Breast Cancer: A Unique Pathologic Entity?

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Washington Hospital Center
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Outline

• Overview
• Therapy
  – High dose chemotherapy
  – NCI – 0173 bevacizumab study
  – Metronomic therapy
  – Lapatinib
• Future Directions
Inflammatory Breast Cancer

- Rare, 2% in U.S., higher in other countries
- Most aggressive form of breast cancer

- Clinical diagnosis
  - diffuse erythema
  - *peau d’orange*
  - often no palpable mass
Locally advanced breast carcinoma (IBC and LABC)

- There is a long-standing debate concerning whether IBC and LABC reflect an advanced breast cancer continuum or discrete clinicopathologic entities?

Inflammatory Breast Cancer

- Small increased incidence in US over 30 years
- Higher incidence in Blacks than Whites
- Younger age than non-IBC
- Weak association with pregnancy/lactation, family history, and larger BMI
- Tunisian studies link increased incidence: rural residence, hyperimmune response, and MMTV

Mammogram of patient with IBC

Courtesy of C. Chow
Inflammatory Breast Cancer

- Dermal lymphatic invasion (Not required)
- No increased inflammatory cells
- More frequently ER/PR negative Her-2/neu positive
- TNM - T4d - “majority of breast”
Inflammatory Breast Cancer
Standard Treatment

Primary Chemotherapy*

\[ \downarrow \]

Mastectomy

With delayed reconstruction

\[ \downarrow \]

RT

\[ \downarrow \]

Hormonal Therapy

*Trastuzumab for HER2 positive tumors
# Survival and Prognosis of IBC: Single Institution Experiences

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>Regimen</th>
<th>Median survival (months)</th>
<th>5 yr</th>
<th>10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson</td>
<td>178</td>
<td>FAC</td>
<td>37</td>
<td>40%</td>
<td>33%</td>
</tr>
<tr>
<td>Centre H. Becquerel</td>
<td>178</td>
<td>AVCF, FAC, FEC</td>
<td>37</td>
<td>32%</td>
<td>23%</td>
</tr>
<tr>
<td>Institut Gustav Roussy</td>
<td>230</td>
<td>RT +/- AVM/VCF, AVCMF</td>
<td>36</td>
<td>42-74% at 4 years</td>
<td></td>
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</tbody>
</table>
IBC Survival: NCI MB 198

- Non-Inflammatory (42%)
- Inflammatory (20%)

Years from On-Study Date

All breast cancer cases

A: Year after diagnosis

% surviving free of breast cancer death

ER Positive

ER Negative

B: Year after diagnosis

Percent annual hazard rate

All breast cancer cases

Inflammatory breast cancer

C: Year after diagnosis

% surviving free of breast cancer death

D: Year after diagnosis

Percent annual hazard rate

Inflammatory breast cancer

British Columbia: Population-Based Survival Analysis

• Retrospective study from 1980-2000 of 485 IBC patients – 1/3 metastatic at diagnosis
• In 308 pts - more intensive chemo improved survival (data limited)
• Mastectomy improved local control: LRFS 59-63% with Mx and 34% without

Panades, J Clin Oncol 23:1941, 2005
## High Dose Chemotherapy in IBC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>pCR(%)</th>
<th>OS(%)</th>
<th>yrs</th>
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<tbody>
<tr>
<td>Viens</td>
<td>100</td>
<td>32</td>
<td>70</td>
<td>3</td>
</tr>
<tr>
<td>Adkins</td>
<td>47</td>
<td>3</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td>Bertucci</td>
<td>74</td>
<td>27</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>Somlo</td>
<td>120</td>
<td>NA</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Ayash</td>
<td>50</td>
<td>14</td>
<td>64</td>
<td>2.3</td>
</tr>
<tr>
<td>Dazzi</td>
<td>21</td>
<td>21</td>
<td>52</td>
<td>4</td>
</tr>
</tbody>
</table>
Molecular characteristics of IBC

- Overexpression of E-Cadherin, MUC1, RhoC- GTPase, and p53
- Loss of LIBC/WISP3 or IGFBP-rp (tumor suppressor gene)
- Increase in angiogenic and lymphangiogenic (VEGFC and D) factors
Increased Microvessel Density in Inflammatory Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>MVD (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBC</td>
<td>45</td>
<td>25.5 (0-110.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Non-IBC</td>
<td>22</td>
<td>6.5 (0-92.5)</td>
<td></td>
</tr>
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</table>

McCarthy et al., Clin Cancer Res 2002; 8: 3857
NCI-0173 – IBC and LABC

Surgery → RT

Hormonal therapy if ER+

Correlative studies
- Dynamic Contrast Enhanced MRI (DCE-MRI)
- Tumor Biopsies (mammotome)

\[ \text{Docetaxel 75 mg/m}^2 \]
\[ \text{Doxorubicin 50 mg/m}^2 \]
\[ \text{Bevacizumab 15 mg/kg} \]

Wedam et al., J Clin Oncol 2006; 24:769
NCI-0173 Responses to Bevacizumab and Chemotherapy

Total Patients: N= 21

- Partial Response: 14 (67%)
  - Pathologic CR: 1
- Stable Disease: 5 (24%)
- Progressive Disease: 2 (9%)

Wedam et al., J Clin Oncol 2006; 24:769
<table>
<thead>
<tr>
<th>Marker</th>
<th>Baseline</th>
<th>Change</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67</td>
<td>+2% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVD</td>
<td>-15% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF-A</td>
<td>-50% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGFR2</td>
<td>+70% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pVEGFR2 (Y996)</td>
<td>-69% (0.024)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pVEGFR2 (Y951)</td>
<td>-67% (0.004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUNEL</td>
<td>+129% (0.0008)</td>
<td></td>
<td></td>
</tr>
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</table>
NCI-0173 DCE-MRI Time Intensity Comparisons

Increased uptake of contrast in tumor reflecting permeability and flow

Wedam et al., J Clin Oncol 2006; 24:769
Excellent clinical response to combined anti-angiogenic and chemotherapy

Correlative studies after bevacizumab
- Decrease in phospho-VEGFR2 (tumor cells)
- Increase in tumor apoptosis (tumor cells)
- Decrease in vascular permeability + flow on DCE-MRI

Gene expression profiling in process for IBC signature

Wedam et al., J Clin Oncol 2006; 24:769
SWOG 0012
Conventional vs Metronomic Schedule

5 X AC q 3 wk
(DI 20, 200)
→ paclitaxel wkly x 12

A qwk + C qd X 15 wks
(DI 24, 420) + GCSF
→ paclitaxel wkly x12

Ellis, et al ASCO 2006
SWOG 0012

• Accrual: 10/ 2002 – 12/2005
• Eligibility: locally advanced breast cancer, 372 patients randomized
• 265 evaluable for primary outcome, 132 arm 1, 133 arm 2, including those who did not proceed to surgery
  – 81 pts with IBC
SWOG 0012: Conclusions

- **Arm 1 AC → P**: pCR* 19%  
  - pCR+N0 15%
  - OR = 2.11  
  - 95% CI = 1.13 - 3.96, p = 0.020

- **Arm 2 AC+G → P**: pCR 31%  
  - pCR+N0 26%

Inflammatory Breast Cancer

- pCR: 12%  
  - 32%
Responses seen in IBC Phase I lapatinib studies
EGF103009 Lapatinib Refractory/Relapsed IBC Study Schema

- **Cohort A**
  - HER2+
  - Pre-treatment tumor biopsy
  - Administer lapatinib (1500 mg/d)
  - RECIST criteria and *chest wall/skin response documented by Canfield digital photography
  - Post-treatment Biopsy Day 28

- **Cohort B**
  - HER1+/HER2-

*Trudeau et al., ESMO 2006C*
## EGF103009 Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>53 (32-79)</td>
</tr>
<tr>
<td>Dermal lymphatic invasion</td>
<td>75%</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>21%</td>
</tr>
<tr>
<td>IV</td>
<td>79%</td>
</tr>
<tr>
<td>Median chemo regimens</td>
<td>4.5 (0-21)</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>98%</td>
</tr>
<tr>
<td>Anthracycline/Taxane</td>
<td>78%</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>75% (Cohort A)</td>
</tr>
<tr>
<td>Sites</td>
<td></td>
</tr>
<tr>
<td>North America/Israel/EU</td>
<td>71%</td>
</tr>
<tr>
<td>Tunisia</td>
<td>29%</td>
</tr>
</tbody>
</table>

*based on data from 49 patients; efficacy/safety data from 47 patients

*Trudeau et al., ESMO 2006*
EGF103009 Response Rate to Lapatinib Monotherapy

- Skin - 17 CR/PR
- RECIST - 9 PR

Trudeau et al., ESMO 2006
Biomarker Characterization of Responders to Lapatinib

- HER2 (ErbB2) (FISH+/IHC 3+): 94%
- pErbB-2: 80%
- ER+: 29%
- IGF-1R: 100%
- PTEN deficient (IHC 0 or 1+): 73%
- mutant p53: 36%

Trudeau et al., ESMO 2006
EGF102580 Lapatinib Plus Paclitaxel as Neoadjuvant Therapy in Newly-Diagnosed Inflammatory Breast Cancer

Cohort A: HER2 overexpressors

Cohort B: HER2 non-overexpressors

Lapatinib Monotherapy x 14 days

Pre-dose Tumor Biopsy

12 weeks
IV Paclitaxel 80 mg/m²/week
+ Lapatinib 1500 mg PO once daily

Combination Therapy

Surgical Resection

Tumor Tissue (250 mg) at time of Surgical Resection
Assessment of pCR Biomarker Analysis

Cristofanilli, SABCS 2006
## Objective Response Rates

**Clinical Skin/Chest Wall Responses**

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Cohort A (HER2+)</th>
<th>Cohort B (HER2-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>3 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>20 (67%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>3 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>0</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (13%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Response Rate (CR or PR)**

- Cohort A: 77%
- Cohort B: 80%

**Clinical response to lapatinib monotherapy (d14)**

- Cohort A: 10 (30%)
- Cohort B: 0

**Pathological Complete Responses**

- Cohort A: 3/18 (17%)
- Cohort B: 0/3

*Defined as no evidence of residual invasive tumor, including no residual tumor in the axillary lymph nodes*
Functional Imaging to Evaluate Response to Lapatinib
Biomarker Analyses

IBC Phenotype

Candidate Predictors of Response to Lapatinib

% Patients

Cohort A
Cohort B

ER  PR  E-Cad  p53  RhoC

ErbB1  ErbB2  ErbB3  IGF1R  PTEN  HRG  TGFα

phosphorylated
Lapatinib in IBC

- Short course has 30% RR in previously untreated patients
- Monotherapy has 50% RR in heavily pretreated patients
- Activity almost exclusively in pts with HER2 positive disease
- Responses seen with PTEN deficiency or mutant p53
Molecular Profiling of IBC

- 109 gene signature – over expression of basal phenotype
- NFκ-B overexpression
- Her-2/neu overexpression
- 16 pathways and 61 GO categories discriminate from non-IBC

RT-PCR
- 27 upregulated genes
- Increased expression of angiogenesis and lymphangiogenesis related genes

Summary

• IBC is a rare disease with poor prognosis
• Anti-angiogenic therapy results in direct tumor effect
• Lapatinib effective in HER2 positive IBC
• Important to define molecular signature of IBC and predictors of response