Special Issues in Locally Advanced Breast Cancer (LABC): Medical Oncology Perspective

Stephen Chia MD, FRCPC
Medical Oncologist
British Columbia Cancer Agency
Outline

• Staging for locally advanced breast cancer
• Inclusion of ipsilateral supraclavicular (N\textsubscript{3c}) involvement as LABC
• Systemic trials specific for LABC
• Role of radiation in LABC
Goals of Primary Systemic Therapy for LABC

- Recommendations of International Expert Panel on Use of Neoadjuvant Systemic Treatment Operable Breast Cancer
- In population of LABC:
  1º aim: Improve surgical options
  2º aims: Obtain freedom from disease
  Gain information on tumor response

Natural History of LABC

- LABC first recognized as disease not cured by surgery by Haagensen and Stout in 1943
- Retrospective study of 454 consecutive patients with $T_{3-4}N_xM_0$ treated with RT from 1968-1972
  - No neo/adjuvant systemic therapy given
  - 133 selected patients underwent radical mastectomy
  - 72% $T_4$ (15% $T_{4d}$)
  - 67% $N_{1-3}$
  - Median survival 2.5 years

Haagensen CD and Stout AP. Ann Surg 1943;118:859-1032
Fig. 2. Survival in relation to presence and extent of regional nodes.
Staging of LABC

• Systematic review of published literature 1966-1998
• In stage III breast cancer recommend chest imaging, liver imaging and bone scan
• Detection of distant metastases in stage III:
  bone scan: 8.3%
  liver U/S: 2.0%
  CXR: 1.7%
• False(+) rates: 10-22% bone scan, 33-66% liver U/S and 0-23% CXR

Myers RE, et al. CMAJ 2001;164:1439-44
FDG PET - Left Breast Cancer Help Determine Extent of Advanced Axillary Disease

SUV_{Max} = 11.1 (coronal slices)

SUV_{Max} = 12.4

Courtesy of DA. Mankoff
Internal Mammary (IM) Node on FDG PET: Locally Advanced Breast Cancer Pre-Therapy
Up to 20% IM nodal disease by FDG PET in LABC

IM uptake predicted:
• Likelihood of failure
• Pattern of failure

IM uptake associated:
• Non-OUQ location
• Inflammatory Br CA

Tumor Location and Risk of Relapse

• Population based analysis of 6,781 women with early stage breast cancer from 1989-1995 comparing outcome of medial to lateral hemisphere tumors

• Despite medial based tumors:
  - smaller in size
  - less LVI
  - less nodal involvement

• Medial location tumors associated with worse outcome:
  - 5 year DDFS: 66.3% vs. 74.2% (p<0.005)

Ipsilateral Supraclavicular Node Involvement

- 6th Edition AJCC Staging for breast cancer changed supraclavicular metastases from $M_1 \rightarrow N_{3C}$
- MD Anderson experience of $n=70$ with ipsilateral SCN treated with combined modality therapy (neoadjuvant anthracycline based chemotherapy) had 10 year DFS of 32%
- British Columbia cohort of ipsilateral SCN ($n=51$) had 10 year BCCS of 24%

Systemic Therapy Trials Specific for LABC

- Initial largest RCT in LABC initiated in 1979 by EORTC assessed adjuvant chemotherapy, hormonal therapy or both in LABC
- N=410 with clinical LABC randomized to:
  - RT alone
  - hormonal therapy (Tamoxifen or OA)
  - CMF x 12 combination
- Mastectomy not part of treatment plan

Systemic Therapy Trials Specific for LABC

- Other initial randomized phase III trials of chemotherapy in LABC failed to show OS improvement BUT:

  small numbers (< 50/arm)
  older chemotherapy regimens (CMF)
  inconsistent staging

All Patients

4 cycles of CVAP

Response

No Response

First Phase

Second Phase

4 cycles of Docetaxel

4 cycles of Docetaxel

4 cycles of CVAP

Large $\geq 3$ cm tumors
$T_3, T_4, T_x N_2$


The Aberdeen Breast Group Neoadjuvant Trial LABC
Survival

- Patients who responded to CVAP
- Randomised to: *docetaxel* x4 or *CVAP* x 4
- Survival increased in docetaxel group

Patient Population (n = 448)

- 40% T4a-c
- 45% T4d
- Locoregional treatment variable

Randomization:

C 75 mg/m² po q d days 1–14
E 60 mg/m² IV days 1 and 8
F 500 mg/m² IV days 1 and 8

q 4 wk x 6

E 120 mg/m² IV day 1
C 830 mg/m² IV days 1
with G-CSF day 2-13

q 2 wk x 6

• In exploratory analysis: PFS worse in IBC (median 23.5 m) vs LABC (median 44 m)

SWOG 0012/CTSU: Neoadjuvant Locally Advanced Breast Cancer Trial
PI: G. Ellis  ASCO 2006

Weekly AC x 15
A 24 mg/m2 weekly
C 60 mg/m2/day
G-CSF (days 2-7)

vs.

Q3 week AC x 5
A 60 mg/m2
C 600 mg/m2

Weekly paclitaxel x 12

surgery

Weekly paclitaxel x 12

Activated 5/1/01
Accrual = 350/350
Anglo-Celtic Cooperative Oncology Group Study:

Patient Population (n = 363)
- T size ≥ 3 cm (operable)
- 15% T4d
- 8% LABC

A 60 mg/m² IV days 1 q 3 wk x 6
C 600 mg/m² IV days 1

A 60 mg/m² IV day 1 q 3 wk x 6
T 75 mg/m² IV days 1

Evans JTR et al. J Clin Oncol 2005;23:2988-95
• With 32 months median F/U no difference in RFS or OS

Table 3. Pathologic Response Rates in Patients Undergoing Surgery to the Breast (n = 342) After Primary Chemotherapy

<table>
<thead>
<tr>
<th>Pathologic Response</th>
<th>AC (n = 172)</th>
<th>AD (n = 170)</th>
<th>All Patients (n = 342)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>No residual disease</td>
<td>26</td>
<td>15</td>
<td>10 to 20</td>
</tr>
<tr>
<td>No residual invasive disease (includes DCIS only)</td>
<td>41</td>
<td>24</td>
<td>17 to 30</td>
</tr>
<tr>
<td>No residual invasive disease and negative axillary lymph nodes</td>
<td>27</td>
<td>16</td>
<td>10 to 21</td>
</tr>
</tbody>
</table>

NOTE. The analyses do not include the 20 patients who did not have surgical intervention on completion of chemotherapy and do not include the one patient who had surgery to the axilla only.

Abbreviations: AC, doxorubicin and cyclophosphamide; AD, doxorubicin and docetaxel; DCIS, ductal carcinoma in situ.

Adapted from Evans JTR et al. J Clin Oncol 2005;23:2988-95
EORTC 10994

First prospective trial assessing the potential value of p53 in patients with locally advanced/inflammatory or large operable breast cancer prospectively randomized to a taxane vs a non taxane regimen (BIG 00-01)

**Trial design**

- LABC or Large Operable Breast Cancer Pts
- 1850 pts
- Randomized
- Biopsies to be taken at baseline:
  1. 1st sample: fixed for histopathological analysis
  2. 2nd sample: snap frozen (2 trucut biopsies with 14G needle)

**Regimens**

- **Non Taxane Arm**
  - Regimen x 6
- **Taxane arm**
  - 3xT + 3xET

**LocoR TRT**

Courtesy of M. Piccart
Normal p53 Activates Transcription and Mutations Abolish Function

1. RT-PCR
   p53 mRNA
   2. Gap Repair
   pSS16
   CEN ARS
   LEU2

3. Selection of transformants

   wt p53
   Ade^+ colonies are white
   = wild type p53

   mutant p53
   Ade^- colonies are red
   = mutant p53

Courtesy of H. Bonnefoi – PI EORTC 10994
Radiotherapy Trials Specific for LABC

- Paucity of randomized trials investigating the role of RT in LABC
- To be reviewed by Dr. Buchholz Tues AM (8:00-8:20 AM)
- Data available for Stage III disease is following adjuvant systemic therapy
- Questions to be addressed:
  - timing (prior to or following surgery ?)
  - fields (include IMC ?)
  - sparing a cohort (pCR cohort ?)
Conclusions

• Complete staging in LABC is important with PET scanning potentially adding additional information

• Isolated SCN involvement (N3c) and inflammatory breast cancer (T4D) have different outcomes than LABC (separate trials or stratify)

• Limited number of trials specifically in LABC appear to show:
  - addition of taxane improves outcome
  - dose-intense anthracycline regimen does not improve outcome (but metronomic schedule may)
    - sequential taxane vs. concurrent taxane improves outcome

• Role of RT following neoadjuvant chemotherapy needs to be studied