Chemotherapy in Breast Carcinoma

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Gujarat Cancer & Research Institute,
Ahmedabad.
Breast Cancer Global & Indian Scene

- High rates: 86-104/100,000 in developed countries – exception- Japan
- Risk of developing breast cancer during life time of woman 1 in 14 (upto age 70)
- Decreasing mortality in USA due to early diagnosis and management.
- 20-30/100000 in various population based registries. Lower rates in rural population
- 70,000 to 80,000 new cases per year. About 10% will be below age of 40. Average age: 49
- Higher rate than Cancer cervix in Urban population of Bombay, Delhi, Trivendrum and Ahmedabad
- 12-26% cancer in women in hospital registries
Natural history – if untreated

- Average survival from 1st symptom: 44 months
- Median survival: 2.5 years
- 5 year survival: 22%
- 10 year survival: 5%
- Above data on the basis of tumor doubling time
- Biology of breast cancer: Aggressive or slowly progressive
Breast Cancer-Priority Heath Problem

• 80 to 85% of women after developing their Breast cancer die of their Breast cancer

Breast Cancer Patients Age-wise

- Age Group: <30
  - Number of Patients: 15

- Age Group: 31-40
  - Number of Patients: 79

- Age Group: 40-50
  - Number of Patients: 191

- Age Group: 51-60
  - Number of Patients: 191

- Age Group: 61-70
  - Number of Patients: 108

- Age Group: 71-80
  - Number of Patients: 43

- Age Group: >80
  - Number of Patients: 17

- No. of Pts.
<table>
<thead>
<tr>
<th>Stage</th>
<th>India</th>
<th>West</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0-</td>
<td>12.4%</td>
<td>41.8%</td>
<td>98%</td>
</tr>
<tr>
<td>Stage I-</td>
<td>4% to 8%</td>
<td>33.1%</td>
<td>90%</td>
</tr>
<tr>
<td>Stage II-</td>
<td>40% to 57%</td>
<td>8.0%</td>
<td>70%</td>
</tr>
<tr>
<td>Stage III-</td>
<td>28% to 41%</td>
<td>4.7%</td>
<td>50%</td>
</tr>
<tr>
<td>Stage IV-</td>
<td>6% to 14%</td>
<td>4.7%</td>
<td>4.7%</td>
</tr>
<tr>
<td>39% IIIB and IV in illiterate-against 19% in educated</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Dr. Pankaj Shah's Clinic
Stagewise Distribution

No. Of Pts.

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>36</td>
</tr>
<tr>
<td>IIA</td>
<td>127</td>
</tr>
<tr>
<td>IIB</td>
<td>126</td>
</tr>
<tr>
<td>IIIA</td>
<td>65</td>
</tr>
<tr>
<td>IIIIB</td>
<td>26</td>
</tr>
<tr>
<td>IV</td>
<td>22</td>
</tr>
</tbody>
</table>
5-Year Survival Rates by Stage

- Stage 0 (95%)
- Stage I (88%)
- Stage II (66%)
- Stage III (36%)
- Stage IV (7%)

Management of Breast Cancer

• Ideal example of joint management by all three disciplines.
Goals of Therapy

- Mainly Systemic disease with local presentation
- Early disease= To prevent recurrence – Adjuvant therapy
- For locally advanced disease- Neoadjuvant therapy
- For advanced disease palliation
Treatment Sequences

- Optimum yet to determine
- Local surgery with AND -> Adjuvant CT as per need or FNAC -> Neoadjuvant CT -> Surgery or RT -> CT
Advances in Treatment

1980
Tamoxifen
Mitoxantrone

1990
Doxorubicin
Epirubicin
Paclitaxel
Vinorelbine
Aromatase Inhibitors

2000
Docetaxel
Gemcitabine
Capezitabine
Trastuzumab
Fulvestrant
Albumin-Bound Paclitaxel
Lapatinib
Ixabepilone

CMF = cyclophosphamide, methotrexate, and 5-fluorouracil.
The Cancer Cell in 1975

Nucleus

Question mark

Cytoplasm

M.J. Piccart

Courtesy of T. Tursz
Prognostic and Predictive Factors

- Prognostic factors
  - Predict natural history
    - Nodal status
    - Tumor size
    - LVI
    - Grade
    - HER2 status*
    - ER/PgR*
    - Age
    - Recurrence score*

- Predictive factors
  - Predict response to therapy
    - ER/PgR*
    - HER2*
    - Recurrence score*

*Both prognostic and predictive

LVI = lymphovascular invasion; ER = estrogen receptor; PgR = progesterone receptor.
<table>
<thead>
<tr>
<th>Risk category</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Low risk      | Node negative AND all of the following features:  
• pathological tumour size <2 cm  
• pathological tumour grade 1  
• absence of peritumoural vascular invasion  
• *HER2/neu* gene neither over-expressed nor amplified  
• age >35 years |
| Intermediate risk | Node negative AND at least one of the following features:  
• pathological tumour size >2 cm  
• pathological tumour grade 2–3  
• presence of peritumoural vascular invasion  
• *HER2/neu* gene overexpressed or amplified  
• age <35 years |
| High risk     | Node positive (1–3 nodes involved) AND *HER2/neu* gene neither over-expressed nor amplified  
Node positive (1–3 nodes involved) AND *HER2/neu* gene over-expressed or amplified  
Node positive (4 or more involved nodes) |
Breast cancer = At least 4 distinct diseases!

Sorlie T et al, PNAS 2001

Courtesy of Lisa CAREY
Chemotherapy in carcinoma breast

- Adjuvant
- Neoadjuvant
- Chemotherapy in metastatic cancer
The Generations (Lineages and Chains of Inference)

CMF → CAF, CEF

CMF → FAC

FE(50)C → FE(100)C → CA*4 + P*4 (Q3W)

DAC → FEC*3+D3, CA*4+P*4(Q2W) §

FEC*4+[P*8(Q1W)]?

P = paclitaxel; D = docetaxel; A = doxorubicin; E = epirubicin

§ Exploratory analyses suggest may be less effective in ER+ cases

? Hazard ratios consistent with designation but p values for OS not < 0.05
Adjuvant chemotherapy

CMF, first generation, 1970s
Cyclophosphamide
Methotrexate
5-FU

Benefit in
- Older individual with early stage carcinoma Breast
- Distant recurrence
- Survival
<table>
<thead>
<tr>
<th>Regimen</th>
<th>N=</th>
<th>% Proportional Risk Reduction (standard error)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF</td>
<td>4103/4047</td>
<td>Recurrence: 24 (3) Death: 14 (4)</td>
<td></td>
</tr>
<tr>
<td>CMF + extra cytotoxics</td>
<td>1622/1596</td>
<td>Recurrence: 20 (2) Death: 15 (5)</td>
<td></td>
</tr>
<tr>
<td>Other polychemotherapy</td>
<td>3701/3719</td>
<td>Recurrence: 25 (4) Death: 17 (4)</td>
<td></td>
</tr>
<tr>
<td>Average Polychemotherapy</td>
<td>9426/9362</td>
<td>Recurrence: 24 (2) Death: 15 (2)</td>
<td></td>
</tr>
</tbody>
</table>

* Number of patients in the trials who received polychemotherapy vs the number who did not.

† Two times the SE defines the ~ limits of the 95% confidence interval.
Adjuvant chemotherapy

- **CAF or CEF, 2nd generation, 1980s**
  - Cyclophosphamide
  - Adramycin (or Epirubicin)
  - 5-FU
  - More toxic than CMF
  - CAF better than CMF in high-risk group
    - Axilla LN+
    - LN-, but tumor large or other risk factor
Table 5. Proportional Risk Reduction of Adverse Outcome for Patients Treated with Adjuvant Anthracycline vs Non-Anthracycline Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N=</th>
<th>% Proportional Risk Reduction (standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Anthracyclines vs without</td>
<td>3477/3473</td>
<td>Recurrence 12 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death 11 (5)</td>
</tr>
</tbody>
</table>
What have we learned?

- Standard regimens are CMF and CAF
- Anthracycline (e.g. Adriamycin) containing regimens are superior to those that lacks it
- High dose therapy did not improve overall survival
  - Increased morbidity and mortality

After 200+ RCTs -

- Combination therapy is superior to single agents
- 4 to 6 months produced optimal results
  - Longer treatment with the same regimen did NOT provide incremental gains
- Hormone receptor-positive patients benefit from sequential chemotherapy plus endocrine therapy
  - Additive therapeutic effect
Third Generations Regimen
Taxanes as Adjuvant Therapy in BC

- Taxane use in stage I-III BC significantly improves disease-free survival and overall survival.
- Recurrence is still a substantial problem.
- Emergence of molecular resistance to taxanes.
- Increases population requiring alternate therapy.
- Decreases efficacy to other chemotherapies by cross-resistance.

BC = breast cancer.
Taxane Mechanism of Action
(Paclitaxel, Docetaxel)

- Stabilize microtubules and promote polymerization
- Arrest cellular division at G2/M checkpoint, inducing apoptosis
- Reversibly bind β-tubulin subunits

Esteva et al. Oncologist 2001;6:133.
Taxanes

- 1st Trial CALGB 9344: AC + paclitaxel(T)
- 3,121 node-positive patients
- Median follow-up of 69 months
- 5 yr DFS: 70% v 65%, p=0.0023
- 5 yr OS: 80% v 77%, p=0.0064

Docetaxel (Taxotere) Trial

- **BCIRG 001 Trial**
  - 1,491 node-positive patients
  - TAC X6 v FAC X6
  - 5 yr outcome
    - DFS: 75% v 68%
    - OS: 87% v 81%
  - Increased morbidity
    - Febrile neutropenia 10X control arm
    - Neurotoxicity

Dose-dense Regimen

- **Theoretical premise:**
  
  "Full doses of drug, given at the highest possible frequency, will produce the highest degree of cell kill"

- **CALGB 9741**
  
  - 2,005 node-positive patients
  
  - 2 x 2 factorial design
    
    - A → T → C every 3 weeks
    - A → T → C every 2 weeks + G-CSF
    - AC → T every 3 weeks
    - AC → T every 2 weeks + G-CSF
CALGB 9741

- Median follow-up of 36 months
- Dose dense regimen
  - 4 yr DFS: 82% v 75%
  - Significant OS in favor of dose-dense arm
  - Low rate of neutropenic fever and cardiac toxicity
  - Increased rate of anemia

<table>
<thead>
<tr>
<th>Trial</th>
<th>No.</th>
<th>Follow-up</th>
<th>Regimen</th>
<th>Overall survival</th>
<th>5-year absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9344</td>
<td>3121</td>
<td>69</td>
<td>AC x 4 → T x 4</td>
<td>HR 0.82, p 0.006</td>
<td>OS 80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.71–0.98)</td>
<td></td>
</tr>
<tr>
<td>NSABP B-28</td>
<td>3060</td>
<td>64</td>
<td>AC x 4 → T x 4</td>
<td>HR 0.93, p 0.46</td>
<td>OS 85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AC x 4</td>
<td>(0.78–1.12)</td>
<td></td>
</tr>
</tbody>
</table>
• TAC is a very effective adjuvant regimen for patients with node-positive breast cancer:
  – Significant improvement of DFS and OS over FAC
  – TAC significantly improved DFS irrespective of nodal, menopausal, HER2 and hormonal status
Conclusions

• Taxanes have improved the effectiveness of several adjuvant regimens
• Until now the backbone of these regimens has been an anthracycline
• Recent evidence relates effectiveness of anthracyclines to topoisomerase IIa
• There are now 2 non-anthracycline regimens that challenge the assumption that anthracyclines are needed to treat breast cancer
Cardiovascular Side Effects of Modern Cancer Therapy

- Arrhythmia
- Cardiac Dysfunction
  - Heart Failure
- AP / MI
- Hypertension
- Thromboembolism
Overall Conclusions

• Two adjuvant breast trials have demonstrated the efficacy of non-anthracycline regimens:
  ✓ USO 9735: TC > AC (HER2 status unknown)
  ✓ BCIRG 006: efficacy of TCH in HER2-positive patients

• Molecular data from BCIRG 006 puts the role of anthracyclines in adjuvant breast cancer treatment into question

• Anthracyclines cause significant cardiotoxicity, which is augmented with trastuzumab

• Optimal way to prevent cardiotoxicity is to eliminate the key stressor: anthracyclines
Adjuvant Endocrine Therapy

- All with ER positive tumors require ET
- Premenopausal women - Tamoxifen
- Postmenopausal women - Aromatase inhibitors
Chemotherapy

- Lower toxicity profile compared to
  - Node-negative: 5% improvement in 10-YR survival
  - Node-positive: 10% improvement in 10-YR survival

- Relative risk reduction of 25%
- 5 years treatment of ER+/PR+ breast cancer
- Anti-estrogen receptor

Gold Standard: Tamoxifen (Nolvadex)
Aromatase Inhibitors (AIs)

- Conversion of androgenic substrates to estradiol
  - Enzyme complex - aromatase
    - Highly expressed in ovarian follicles in premenopausal women
- AIs blocks aromatase activity
- Postmenopausal women:
  - Residual estrogen production by peripheral conversion
    - Subcutaneous fat, liver, muscle
  - AIs suppress circulating estrogen by 98+\%
AIs and Breast Cancer

- Estrogen and receptor positive breast carcinoma
- Tamoxifen binds estrogen receptors and exerts anti-estrogenic effect
- AIs block peripheral estrogen conversion in postmenopausal women
- Reduction in estrogen results in cancer growth inhibition
- AIs have minimal effect on breast cancer in premenopausal women in clinical trials
Adverse Effects: AIs v Tamoxifen

- Lower incidence
  - Hot flashes
  - Vaginal bleeding and discharge
  - Venous thromboembolism
  - Endometrial cancer

- Higher risk for
  - Musculoskeletal symptoms
  - Fractures associated with osteoporosis

Fulvestrant

- Pure estrogen antagonist
- Monthly intramuscular injection
- Activity in tamoxifen resistant and AI-resistant advanced breast cancer.
Role of Ovarian ablation\suppression

- Premenopausal women
- Can be achieved through surgery or ovarian irradiation or through the use of LHRH agonists.
- No added advantage over tamoxifen.
- Useful in Premenopausal women who retain menstruation after chemotherapy.
Tamoxifen

Should be considered in addition to 5 years of
difficulties with Tamoxifen
Should be considered for women having
osteoporosis
Slightly better adverse effects profile except for
Lowering contralateral second primary cancer
Reducing/delaying cancer recurrence
Superior to Tamoxifen
In postmenopausal women, also appears to be

Take Home Message
Role of Biphosphonates

• Premenopausal women with hormone-responsive, stage I and II breast cancer: ABCSG-12 study.

• Endocrine therapy plus ZOL significantly reduces the risk of DFS events by 36% and the risk of RFS events by 35% compared with endocrine therapy alone in premenopausal women with endocrine-responsive BC.
ZA-Mediated Mechanisms Contributing to Improved DFS

Direct antitumor activity

Immune activation

↓ Bone mets recurrence

↓ Nonbone mets recurrence

↓ Contralateral recurrence

↓ Locoregional mets recurrence

↑ DFS

Gene Expression Profiling

Unfixed sample of tumor tissue

Surgical removal of tumor tissue

Tumor RNA

Labeled control cDNA or cRNA

Labeled tumor cDNA or cRNA

DNA microarray

Comparative analysis of gene expression

Molecular signature

Poor prognosis

Good prognosis
Oncotype Dx
MammoPrint (70 Gene Panel)
Breast Cancer Data From the Annual Clinical Oncology Meeting

Refined NSABP / Genomic Health Gene Set

Proliferation Genes
Ki67, STK15, Survivin, Cyclin B1, MYBL2

ER Related Genes
ER, PR, Bcl2, SCUBE2

Her2 Related Genes
Her2, GRB7

Invasion Related Genes
Stromolysin 3, Cathepsin L2

Other Cancer Related Genes
GSTM1, CB68, BAG 1

Reference Genes
Beta-Actin, GAPDH, RPLPO, GUS, TRFC
Breast Cancer Data From the Annual Clinical Oncology Meeting

Refined NSABP / Genomic Health Gene Set

1.04 * Proliferation Gene Group Score
-0.34 * ER Group Score
+ 0.47 * Her2 Group Score
+ 0.10 * Invasion Group Score
-0.08 * GSTM1 + 0.05 * CD68 - 0.07 * BAG1

Prognostic Score
Low Risk < 18
Intermediate Risk 18 - 30.9
High Risk ≥ 31
Survival Analysis by Gene Expression profiling for lymph-node-negative breast cancer patients
Triple-Negative Breast Cancer

- More aggressive clinical course than other forms of breast cancer
- Increased likelihood of distant recurrence
- Increase in node positivity
- Tendency to develop visceral metastases early in the course of their disease
A NEW WAVE OF SUCCESSFUL TARGETED THERAPEUTICS!!!!
Targeted therapy in cancer

• Many more biologic processes understood at a molecular level in the host (the body’s response to the cancer) as well as those in the tumour itself.
### A summary of four adjuvant trials of trastuzumab at time of interim analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility – all patients</th>
<th>No.</th>
<th>Study design</th>
<th>Median follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP-31</td>
<td>LN-positive</td>
<td>1021</td>
<td><strong>Group 1:</strong> AC x 4 → paclitaxel x 4</td>
<td>28 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1022</td>
<td><strong>Group 2:</strong> AC x 4 → paclitaxel x 4 plus weekly trastuzumab for 12 months</td>
<td></td>
</tr>
<tr>
<td>N9831</td>
<td>LN-positive and high risk</td>
<td>1633</td>
<td><strong>Group A:</strong> AC x 4 → weekly paclitaxel x 12</td>
<td>18 months</td>
</tr>
<tr>
<td></td>
<td>LN-negative</td>
<td></td>
<td><strong>Group B:</strong> AC x 4 → weekly paclitaxel x 12 → weekly trastuzumab for 12 months*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1633</td>
<td><strong>Group C:</strong> AC x 4 → weekly paclitaxel x 12 plus weekly trastuzumab for 12 months</td>
<td></td>
</tr>
<tr>
<td>HERA</td>
<td>LN-positive or LN-negative</td>
<td>1694</td>
<td><strong>Group A:</strong> 3 weekly trastuzumab for 24 months*</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>(tumour &gt;1 cm) and completed adjuvant chemotherapy</td>
<td>1694</td>
<td><strong>Group B:</strong> 3 weekly trastuzumab for 12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1693</td>
<td><strong>Group C:</strong> observation</td>
<td></td>
</tr>
<tr>
<td>BCIRG-006</td>
<td>LN-positive or high-risk node negative disease</td>
<td>1073</td>
<td><strong>Group 1:</strong> AC x 4 → docetaxel x 4</td>
<td>23 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1074</td>
<td><strong>Group 2:</strong> AC x 4 → docetaxel x 4 plus weekly trastuzumab then 3 weekly for 12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1075</td>
<td><strong>Group 3:</strong> docetaxel plus carboplatin x 6 plus weekly trastuzumab then 3 weekly for 12 months</td>
<td></td>
</tr>
<tr>
<td>Endpoints</td>
<td>B-31 and N9331</td>
<td>HERA</td>
<td></td>
<td></td>
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<td>-----------</td>
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<tr>
<td></td>
<td>DFS</td>
<td>OS</td>
<td>DFS</td>
<td>OS</td>
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<tr>
<td>Control</td>
<td>133</td>
<td>261</td>
<td>127</td>
<td>220</td>
</tr>
<tr>
<td>T</td>
<td>82</td>
<td>92</td>
<td>29</td>
<td>37</td>
</tr>
<tr>
<td>HR</td>
<td>0.48 (0.39-0.59)†</td>
<td>0.67 (0.48-0.93)‡</td>
<td>0.54 (0.43-0.67)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* † p < 0.0001, ‡ p = 0.015

A summary of the endpoints of the adjuvant trials (NSABP B-31 and N9331, and HERA)
COMBINATIONS OF TARGETED THERAPIES

HER2

T + Lapatinib

ALTTO
BIG-TBCI

HER1

T + Gefetinib

BCRIG 006R/
NSABP-B31R

IGF-1R

T + Anti IGF-1R

TOWARDS an accelerated CURE for HER2+ B.C.?

VEGF

T + Bevacizumab

ER

T + Tam/Al

mTOR

T + RAD 001

T = trastuzumab

Adapted from G. Sledge
THE ALTTO TRIAL

8000 women with HER2 positive breast cancer

CHEMOTHERAPY

Trastuzumab x 1y
Lapatinib x 1y
Trastuzumab then lapatinib
Trastuzumab combined with lapatinib

With a huge translational research effort!
(e.g. tumor / blood collection → back to the lab!)

M.J. Piccart
• ER +ve/ PR +ve, Her2 neu +ve = chemotherapy + Harmonal + Transtuzumab
• ER +ve/ PR +ve, Her2 neu -ve = chemotherapy + Harmonal
• ER +ve/ PR + ve, Her2 neu + ve = chemotherapy + Transtuzumab
• ER -ve/ PR -ve, Her2 neu -ve = chemotherapy
Neoadjuvant Chemotherapy (cont.)

- **Goals**
  - Decrease tumor size
  - Minimize surgery
  - Establish tumor sensitivity

- **Appropriate treatments**
  - Chemotherapy
  - Tamoxifen or aromatase inhibitors
  - Radiation therapy
Factors Influencing Decision to Use Neoadjuvant Chemotherapy in Operable Breast Cancer

- Does the patient need adjuvant chemotherapy based on information known prior to surgery?
- Would neoadjuvant chemotherapy potentially alter the extent of resection?
- Does the patient desire breast preservation?
- Would treatment benefit from knowledge of in vivo chemosensitivity?
Advantages

- Higher rate of breast conservation
  - Convert some “inoperable” breast cancer to potentially curative surgical candidates

- Response in real time
  - Lack of response – change regimen

- Prognosis can be refined by degree of residual disease
  - Pathologic clinical response had much higher DFS and OS

Conclusions

• Neoadjuvant chemotherapy is recommended for patients with locally advanced disease

• A taxane should be included in the regimen

• Ongoing trials will help determine appropriate regimens and the benefit of targeted therapies in this setting
Trials of Neoadjuvant Trastuzumab: Summary of Efficacy

- Preoperative clinical responses observed
  - Overall response rate, 70% to 90%
  - Clinical complete response, 15% to 30%
  - Pathologic complete response, approximately 18%

- Responses higher for patients with 3+ expression of HER2
Metastatic Breast Cancer

- Chronic disease
- MS of MBC-2 to 3 yrs/5-10% live more than 10 yr.
- 3% to 25% can achieve CR/PR and can be rendered disease free and progression free for more than 5 yrs.
- Optimal sequential use of all modalities can lead to maximum palliation, delay progression and death as much as possible
When to initiate CT in MBC?

• Difficult decision
• There is no evidence that CT should be initiated as soon as MBC is identified
• Optimal duration of CT also varies on the basis of clinical situation and patient preferences
Chemotherapy Regimens for MBC: 2008 NCCN Recommendations

**Representative Single Agents**
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin
- Paclitaxel
- Docetaxel
- Capecitabine
- Vinorelbine
- Gemcitabine
- Albumin-bound paclitaxel

**Combination Regimens**
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

MBC = metastatic breast cancer; F = fluorouracil; A = doxorubicin; C = cyclophosphamide; E = epirubicin; T = paclitaxel; M = methotrexate.

# First-Line MBC: Single-Agent Response Rates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel\textsuperscript{1} (75-100 mg/m\textsuperscript{2})</td>
<td>40-68</td>
</tr>
<tr>
<td>Paclitaxel\textsuperscript{1} (175-250 mg/m\textsuperscript{2} 3-24 h)</td>
<td>32-62</td>
</tr>
<tr>
<td>Doxorubicin\textsuperscript{2}</td>
<td>43</td>
</tr>
<tr>
<td>Capecitabine\textsuperscript{3}</td>
<td>30</td>
</tr>
<tr>
<td>Vinorelbine\textsuperscript{4}</td>
<td>35-53</td>
</tr>
<tr>
<td>Gemcitabine\textsuperscript{5}</td>
<td>18-37</td>
</tr>
<tr>
<td>Cyclophosphamide\textsuperscript{2}</td>
<td>36</td>
</tr>
<tr>
<td>Fluorouracil\textsuperscript{2}</td>
<td>28</td>
</tr>
<tr>
<td>Methotrexate\textsuperscript{2}</td>
<td>26</td>
</tr>
<tr>
<td>Mitoxantrone\textsuperscript{2}</td>
<td>27</td>
</tr>
</tbody>
</table>

ORR = overall response rate.

Other Modalities Used in the Treatment of Metastatic Breast Cancer

Monoclonal antibody therapy
  Trastuzumab
Bisphosphonate therapy
  Pamidronate
Radiation therapy
Monoclonal Antibody Therapy for Breast Cancer: Conclusions

- Bevacizumab improves PFS when added to paclitaxel for treatment of locally recurrent or metastatic disease
  - Improved overall survival and overall response
  - Increased hypertension, proteinuria, neuropathy with bevacizumab
- Adjuvant trastuzumab improves survival outcomes
- Trastuzumab added to paclitaxel as adjuvant therapy following doxorubicin/cyclophosphamide prolongs disease-free and overall survival
  - Concurrent trastuzumab/paclitaxel appears superior to sequential
- Increased cardiac toxicity in patients receiving trastuzumab + paclitaxel: within 4% acceptable range
Changes in Primary Vs Metastatic Lesions: Results and Summary

Results

- 160 tumor blocks with adequate tissue
  - 115 (72%): no changes in ER/PgR or HER2 status
- Of the 45 (28%) tumors with changes in receptor status
  - 11 (7%): local recurrence
  - 34 (21%): regional or distant relapse
    - 11 went from ER/PgR+ to ER/PgR-
    - 14 went from ER/PgR- to ER/PgR+
    - 3 went from HER2- to HER2+
    - 6 went from HER2+ to HER2-

Summary

- Biopsies of relapsed/metastatic breast cancer should be performed routinely because of changes in ER/PgR or HER2 receptor status

Total Blockade of HER2 May Provide Greater Antitumor Activity and Overcome Resistance

Treatment Efficacy: Lapatinib vs Lapatinib + Trastuzumab

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>Lapatinib (n = 145)</th>
<th>Lapatinib + Trastuzumab (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, %* (95% CI)</td>
<td>6.9 (3.4-12.3)</td>
<td>10.3 (5.9-16.4)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td>1.5 (0.6-3.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P = .46)</td>
</tr>
<tr>
<td>Clinical benefit rate, %† (95% CI)</td>
<td>12.4 (7.5-18.9)</td>
<td>24.7 (17.9-32.5)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td>2.2 (1.2-4.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P = .01)</td>
</tr>
</tbody>
</table>

*Confirmed CR + PR.
†CR + PR + SD \(\geq 6\) mos.

PFS: Lapatinib vs Lapatinib + Trastuzumab

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib (n = 145)</th>
<th>Lapatinib + Trastuzumab (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressed or died, n</td>
<td>128</td>
<td>127</td>
</tr>
<tr>
<td>Median, wks</td>
<td>8.1</td>
<td>12.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.57-0.93)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.008</td>
<td></td>
</tr>
</tbody>
</table>

AVADO Trial PFS: by Bevacizumab Dose

Placebo + docetaxel (n = 241)  Bev 7.5\(^\dagger\) + docetaxel (n = 248)

<table>
<thead>
<tr>
<th></th>
<th>HR + 95% CI (unstratified)</th>
<th>HR + 95% CI (stratified*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.79 (0.63-0.98)</td>
<td>0.69 (0.54-0.89)</td>
</tr>
</tbody>
</table>
| *Data censored for non-protocol therapy prior to PD.*

Placebo + docetaxel (n = 241)  Bev 15\(^\dagger\) + docetaxel (n = 247)

<table>
<thead>
<tr>
<th></th>
<th>HR + 95% CI (unstratified)</th>
<th>HR + 95% CI (stratified*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.72 (0.57-0.90)</td>
<td>0.61 (0.48-0.78)</td>
</tr>
<tr>
<td>*P = .0036</td>
<td></td>
<td>*P &lt; .0001</td>
</tr>
</tbody>
</table>

Median, mos 8.0 8.7


\(\dagger\) mg/kg Q3W.
Rationale for New Agents

- MBC remains an important medical problem
- Anthracyclines and taxanes are the standard of care
  - Increasing use in the adjuvant setting
  - Drug resistance
- Need for new agents
- Capecitabine approved for use after failure of anthracyclines and/or taxanes
  - ORRs 9% to 14% in phase 3 studies\(^1,2\)
- Limited efficacy of other agents used in MBC

Treatment options for bone metastases

- Radiotherapy - treatment of choice for painful bone met. No impact on survival
- Cytotoxic chemotherapy and hormonal therapy tend to prolong survival modestly
- Biphosphonates, gallium nitrate and calcitonin as osteoclast inhibitor
Bisphosphonates in bone metastases

• Pain relief
• Decrease in bone metastases related complications
• Healing of bone met. Lesions
• Preliminary results suggest use of bisphosphonate in patients without over bone met can reduce incidence of bone met.
Radioactive isotopes

- FDA approved: Stronium 89, Samarium 153
- Under active clinical investigations: tin117, yttrium90, rhenium -186, holmium 60
- Produce substantial pain relief in 50% to 80% of patients
- Major toxicity myelosupression
- Useful when symptomatic multiple osseous met inpatient receiving 2nd or 3rd line of systemic therapy
Defining “High Risk” Patients

- What exactly is the relative risk when there is a family history of breast cancer?
- One family member with postmenopausal breast cancer
- 2-3 fold relative risk elevation
- Multiple 1st degree relatives
- Pre-menopausal breast cancer
- Bilateral breast cancer
- Male breast cancer
- Ovarian cancer
The BReast CAncer (BRCA) Genes

- 5 to 10% of breast cancer are hereditary
  - BRCA1
  - BRCA2
- 50% to 80% lifetime risk
- Tumor suppressor genes
  - Involved in cell cycle control
- In addition to breast cancer
  - BRCA1 mutation is associated with 50% risk for ovarian cancer
  - BRCA2 mutation is associated with increased risk for male breast CA
BRCA Genes

- Who should be considered for BRCA testing?
  - 2 first degree relatives
  - One first degree relative
    - Premenopausal
    - Bilateral
  - Ovarian cancer
  - Multiple breast cancer, including male breast cancer
- Offered with complete genetic/social counseling
Chemoprevention

- NSABP BPCT-1
  - 13,388 women randomized to receive tamoxifen versus placebo
  - At median follow-up of 54 months
    - 49% reduction of invasive breast cancer
    - 50% reduction of non-invasive breast cancer
- Caveats
  - No reduction in ER negative carcinomas
  - Overall survival was not a measured outcome
    - We Don’t Know If The Breast Cancer Reduction Translates into Cancer Death Reduction
  - Increased risk for
    - endometrial cancer (RR = 4 in age>50)
    - DVT (RR = 1.7)
    - PE (RR=3.0)

Fisher, JNCI, 1999
STAR Chemoprevention Trial
(Study of Tamoxifen against Raloxifene)

• Tamoxifen vs. Raloxifene
  – both are approved medications that selectively block estrogen receptors
  – estrogen receptors are present on many tissues - breast, bone, uterus, blood vessels, and many others
  – Tamoxifen - breast cancer medication
  – Raloxifene - anti-osteoporosis medication

• Compare the 2 groups of women for development of breast cancer, possible side effects or other benefits
Mean follow-up of 3.9 years, Raloxifene vs Tamoxifen.

- No difference in invasive cancer.
- More cases of non-invasive cancer.
- 84% reduction in endometrial hyperplasia.
- Statistically significant reduction in the number of hysterectomies.
- Reduced endometrial cancers.
- Significantly fewer thromboembolic events and cataracts.
## Cost of chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost(Rs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inj Cyclophosphamide 1 gm</td>
<td>30</td>
</tr>
<tr>
<td>Inj Methotrexate 50 mg</td>
<td>19</td>
</tr>
<tr>
<td>Inj 5fluorouracil 500mg</td>
<td>235</td>
</tr>
<tr>
<td>Inj Adriamycin 50mg</td>
<td>345</td>
</tr>
<tr>
<td>Inj Docetaxel 120mg</td>
<td>3000-10000</td>
</tr>
<tr>
<td>Inj Paclitaxel 300mg</td>
<td>2200- 8000</td>
</tr>
<tr>
<td>Inj Transtuzumab 440mg</td>
<td>1,05000</td>
</tr>
<tr>
<td>Inj Epirubicin 50mg</td>
<td>1350</td>
</tr>
<tr>
<td>Tab Cepecitabine 500mg</td>
<td>68</td>
</tr>
</tbody>
</table>
Average BSA- 1.5

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Cost (Rs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One cycle of CMF</td>
<td>550</td>
</tr>
<tr>
<td>One cycle of FAC</td>
<td>1250</td>
</tr>
<tr>
<td>One cycle of TAC</td>
<td>5000-12000</td>
</tr>
<tr>
<td>One cycle of FEC</td>
<td>4500</td>
</tr>
</tbody>
</table>
Hormonal therapy

- Tamoxifen 2 Rs
- LetraZOLE 5 RS
- Anastrazole – 40 Rs
- Lupride
- Fulvestrant 20000 Rs
Future Perspectives

- ANATOMICAL STAGING - MOLECULAR STAGING
- BIOLOGY OF BREAST CANCER - NEW PROGNOSTIC & PREDICTIVE FACTORS.

PREDICTIVE ONCOLOGY - PREDICTS RESPONSE OF INDIVIDUAL PATIENT TO CT, RT & BIOLOGICAL THERAPY.

ONE SHOE FITS ALL HYPOTHESIS DOES NOT HOLD TRUE ANYMORE