Chemotherapy for Isolated Locoregional Recurrence

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Prognostic factors in patients with isolated recurrences of breast cancer (stage IV-NED)

- Retrospective analysis of 96 patients with isolated recurrence of stage IV breast cancer
- Treatment of loco-regional or distant recurrence was surgery in 18 patients and surgery plus irradiation in 78 patients
- 79 patients received systemic therapy after loco-regional treatment (24 chemotherapy and 55 hormonal therapy)

Juan et al, Breast Cancer Res Treat 1999 Jun;33(2):105-12

RESULTS

Juan et al, 1999

Five-year DFS and OS were 29% and 49%, respectively

Juan et al, Breast Cancer Res Treat 1999 Jun;33(2):105-12
In a multivariate analysis, absence of nodal involvement and systemic therapy were associated with longer DFS

None of the other factors analyzed including menopausal status, T-stage, number of involved nodes, receptor status, adjuvant therapy, sites of first recurrence, or time from mastectomy to first recurrence had a predictive value for DFS and OS.

Locoregional Recurrence
- Associated with increased risk of distant metastases
- Does systemic treatment alter prognosis?
  - Difficult to study in randomized clinical trials
- How aggressively should we treat these patients?
  - Role of chemotherapy and biological therapies still relatively unexplored

Chest Wall Recurrence After Mastectomy
- Low risk: initial node negative disease, time to CWR > 24 mo, radiation for CWR
- Intermediate risk: One or two favorable features
- High risk: No favorable features

Systemic Therapy
- Little data available which answers the question of who should receive systemic therapy, therefore it is usually recommended
- 2001 the Cochrane Review stated that there was insufficient data to suggest that women with local regional recurrence should be treated with chemotherapy and recommended that this should only be considered in the setting of clinical trials

**SAKK 23/82 trial**

Does Systemic Treatment for LRR Affect Survival?

- 167 pts randomized to tamoxifen or observation after complete excision and XRT to recurrence site
  - “Good risk” isolated LRR
    - HR+ (~ 40% unknown ER), DFI > 12 mo and ≤ 3 tumor nodules ≤ 3 cm
    - 79% postmenopausal
  - Median FU 11.6 years
    - DFS 6.5 vs 2.7 years (p=0.03)
    - OS 11.2 vs 11.5 years
    - Tamoxifen appears to have a greater effect on prevention of further locoregional recurrences than distant metastases
    - Tamoxifen had no impact on DFS in pre-menopausal pts


**BIG 1-02/IBCSG 27-02/NSABP B-37**

**METHODS**

- Trial population: Women with previous diagnosis of invasive breast cancer treated by mastectomy or breast-conserving surgery who develop an isolated local and/or regional ipsilateral invasive recurrence
- Excision of all macroscopic tumor without evidence of systemic disease
- Patients are randomized to receive chemotherapy or no chemotherapy
- Radiation, hormonal therapy, and trastuzumab are given as appropriate
- Primary endpoint is disease-free survival (DFS)
- Accrual goal is 977 patients

Results among first 99 pts:

- Sites of recurrence at study entry were: breast (56%), mastectomy scar/chest wall (35%), and regional lymph nodes (9%)
- Two-thirds of patients have ER+ recurrences
- 65% had received prior chemotherapy


**Does addition of trastuzumab impact LRR recurrences?**
HERA Phase III Trial

**HER2+ (IHC 3+/FISH+) N=3300**

- Primary management
  - No trastuzumab
  - Trastuzumab q3w for 1 year
  - Trastuzumab q3w for 2 years

Trastuzumab 8 mg/kg week 1, then 6 mg/kg q3w


NSABP B-31: Phase III Trial

**Node+ HER2+ (IHC 3+/FISH+) N=2700**

- AC q3w × 4
- Paclitaxel q3w × 4
- OR Paclitaxel qw × 12

- Paclitaxel q3w × 4 + trastuzumab qw × 52
- OR Paclitaxel qw × 12 + trastuzumab qw × 52

- Cardiac monitoring: MUGA scans at baseline, post-AC, and 6, 9, and 18 months after R

AC = doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m²; Paclitaxel 175 mg/m² q3w, 80 mg/m² qw; Trastuzumab 4 mg/kg week 1, then 2 mg/kg qw


HERA Results

**Table 3. Efficacy End-Point Events (Intention-to-Treat Groups).**

<table>
<thead>
<tr>
<th>Event</th>
<th>1 Yr of Trastuzumab (N=16994)</th>
<th>Observation (N=16993)</th>
<th>p (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free/survival events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any recurrence, second primary event, or death without prior recurrence</td>
<td>127 (7.5)</td>
<td>220 (13.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>17 (1.0)</td>
<td>37 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>10 (0.6)</td>
<td>13 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Distant recurrence (site)</td>
<td>85 (5.0)</td>
<td>154 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>6 (0.3)</td>
<td>19 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Skeletal</td>
<td>24 (1.4)</td>
<td>38 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>23 (1.2)</td>
<td>15 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Other visceral site</td>
<td>34 (2.0)</td>
<td>82 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>6 (0.4)</td>
<td>7 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Second nonbreast malignant disease</td>
<td>1 (0.2)</td>
<td>6 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Death without prior recurrence</td>
<td>6 (0.4)</td>
<td>3 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>29 (1.7)</td>
<td>37 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Breast-cancer related</td>
<td>23 (1.4)</td>
<td>34 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Without cancer event</td>
<td>6 (0.4)</td>
<td>3 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>1 (0.1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1 (0.1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other cause</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown cause</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>

* Almost 60 percent of the recurrences occurred in patients with estrogen-receptor-negative and progesterone-receptor-negative tumors (48 percent of the study cohort).

N9831: Phase III Trial

**Node+ HER2+ (IHC 3+/FISH+) N=5000**

- AC q3w × 4
- Paclitaxel qw × 12
- Paclitaxel q3w × 4 + trastuzumab qw × 52

- Cardiac monitoring: MUGA scans at baseline, post-AC, post-paclitaxel, and 3 mo after completion of study regimen

AC = doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m²; Paclitaxel 80 mg/m²; Trastuzumab 4 mg/kg week 1, then 2 mg/kg qw

Combined Analysis of Adjuvant Trials

Control Group (n=1880): AC → T
N9831 Group A
B-31 Group 1

Herceptin® (trastuzumab) Group (n=1872): AC → T + H
N9831 Group C
B-31 Group 2

- AC = Doxorubicin/cyclophosphamide 60/600 mg/m² q3w × 4
- T = Paclitaxel 80 mg/m²/wk × 12
- T = Paclitaxel 175 mg/m² q3w × 4 or 80 mg/m²/wk × 12
- H = Herceptin 4 mg/kg loading dose + 2 mg/kg/wk × 51

B-31/N9831 Combined Analysis: Disease-Free Survival

HR = 0.48 (95% CI, 0.39-0.59)
52% relative risk reduction
P<0.0001

B-31/N9831 Interim Analysis: Interim Analysis of Overall Survival

HR = 0.67
33% relative risk reduction
P=NS* at an interim analysis

B-31/N9831 Interim Analysis

Table 2. Sites of First Events.

<table>
<thead>
<tr>
<th>Patients with follow-up</th>
<th>Trial B-31</th>
<th>Trial N9831</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>872</td>
<td>807</td>
</tr>
<tr>
<td>Trastuzumab Group</td>
<td>864</td>
<td>108</td>
</tr>
</tbody>
</table>

Nonsignificant Data on file, Genentech, Inc.
Are there other local and systemic treatment strategies for locoregional recurrence?

HYPERTHERMIA + DOXIL
For Metastatic Breast Cancer of the Chest Wall

- HT is effective against MBC of CW
- Doxil (Liposomal doxorubicin) is effective against MBC
- Doxil accumulation is very high in soft tissue/skin
  - Dose-limiting toxicity occurs in skin (PPE)
- HT potentiates DNA damage (XRT, chemoRx)
- Sequential HT + Doxil may significantly increase Doxil extravasation in heated regions

Park et al, 2002

TOXICITY

- Cohort 1 (HT X 30 min)
  - N = 4 pts, 8 cycles
  - No toxicities
- Cohort 2 (HT X 60 min)
  - N = 23, 82 cycles
- Toxicities
  - PPE in 7 pts (Gr 2) and 1 pt (Gr 3)
  - Mucositis in 4 pts (Gr 2)
  - Thermal burns in 2 pts (Gr 2)
  - CHF in 1 pt (Gr 3)
  - Leukopenia in 4 pts (Gr 2)

EFFICACY OF COMBINED HT/DOXIL

<table>
<thead>
<tr>
<th>RESPONSE TO TREATMENT (HEATED)</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR) – also pCR</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>12</td>
<td>52%</td>
</tr>
<tr>
<td>Minor Response (MR)</td>
<td>3</td>
<td>13%</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>5</td>
<td>22%</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>2</td>
<td>9%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td>OBJECTIVE RESPONSE RATE (RR = CR + PR)</td>
<td>13/23</td>
<td>57%</td>
</tr>
</tbody>
</table>
EFFICACY OF DOXIL ALONE

<table>
<thead>
<tr>
<th>RESPONSE TO TREATMENT</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>1</td>
<td>6%</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>5</td>
<td>28%</td>
</tr>
<tr>
<td>Minor Response (MR)</td>
<td>1</td>
<td>6%</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>5</td>
<td>28%</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>6</td>
<td>33%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>18</td>
<td>100%</td>
</tr>
<tr>
<td>OBJECTIVE RESPONSE RATE (RR = CR + PR)</td>
<td>6/18</td>
<td>33%</td>
</tr>
</tbody>
</table>

EFFICACY OF DOXIL/HT

Example: Pt. #2

PHASE I/II TRIAL OF HYPERHERMIA + DOXIL

Conclusions

- Sequential HT + Doxil chemotherapy:
  - Safe and very well-tolerated
  - No additive or novel toxicities
  - Very active regimen (RR=57%) against metastatic breast cancer of the chest wall
  - Significantly superior to Doxil alone ($p < 0.04$)
  - Consistent with preclinical studies of HT effects on liposome extravasation

Phase II Study of Topical Imiquimod and Weekly Abraxane for the Treatment of Breast Cancer Cutaneous Metastases*

PI: Lupe G. Salazar, MD
Tumor Vaccine Group
University of Washington

For Study Information:
Call Nicole Bates, CCRP, at 866-932-8588
nbates@uw.edu
www.tumorvaccinegroup.org

*Study funded by NIH/NCI R01CA138521-01
**Imiquimod**

- Small molecule immune response modifiers (IRMs)
  - Chemical compounds which generate an immune signal similar to that of pathogenic bacteria
  - Trigger immune activation via toll-like receptor ligands (TLRs) resulting in:
    - Activation of antigen presenting cells
    - Production of pro-inflammatory cytokines with antiviral, anticancer, and immune modulating activities

- Aldara (imiquimod 5% cream)
  - 1st marketed drug in this class (IRMs)
  - Is a TLR-7 agonist with demonstrated clinical activity against genital warts, basal cell cancer and squamous cell cancer

**Imiquimod: Preclinical Studies**

- Imiquimod in neu-transgenic mice (Dr. H. Lu, UW Tumor Vaccine Group)
  - Imiquimod vs placebo cream applied to palpable mammary tumor
    - Imiquimod completely stopped the growth of breast tumors & tumor inhibitory effect persisted after treatment stopped
    - Imiquimod stimulated the secretion of pro-inflammatory cytokines and up-regulated immune co-stimulatory molecules

- Hypothesis: TLR agonists like imiquimod, which have powerful immune properties, can lead to high frequency of cancer rejection in breast cancer patients with chest wall recurrence

**Recurrent Breast Cancer with Cutaneous Metastasis (Hengee et al, 2005)**

65 yr. old woman with local recurrence of cutaneous lesion to back 9 months after initial diagnosis. Initial cancer was ER/PR+ and HER2-. Treated with imiquimod monotherapy.

Pre-Imiquimod

![Irregular inflammatory lesion of left shoulder](image)

Post-Imiquimod

![Invasive cancer cells in a lobular pattern](image)

![Clinical resolution of left shoulder lesion](image)

![Histology shows only fibrosis with mild lymphocytic infiltrate](image)

**Combination Chemo-immunotherapy for Treatment of Breast Cancer Skin Metastasis**

- Phase II Trial of Imiquimod and Abraxane for Treatment of Breast Cancer Skin Metastases
  - Patients with measurable skin lesions refractory to standard therapies
  - Single arm study (n=15) evaluating combination treatment
  - Tumor response rate - 1st objective, Safety/toxicity - 2nd objective
  - Effect on immune response - 3rd objective
  - Treatment: Imiquimod (immunotherapy) + Abraxane (chemotherapy)
    - Abraxane weekly for total of 9 treatments
    - Imiquimod applied topically to target lesions concurrent with Abraxane
    - Lesion measurement, photos, biopsy before & after treatment
    - Post-treatment follow-up every 4 weeks x 12 weeks: tumor and immune response, toxicity
Combination Chemo-immunotherapy for Chest Wall Metastasis

<table>
<thead>
<tr>
<th>Pre-tx Bx</th>
<th>Abraxane</th>
<th>Abraxane</th>
<th>Abraxane</th>
<th>CR/IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Cycle 2</td>
<td>Cycle 3</td>
<td>CR/IR</td>
<td></td>
</tr>
</tbody>
</table>

Q 4 weeks X3 Abraxane

Baseline Cycle 1 Cycle 2 Cycle 3

Salazar and Higgins et al, 2009

Phase 1/2 Study of ThermoDox with Approved Hyperthermia in Treatment of Breast Cancer Recurrence at the Chest Wall (DIGNITY)

Celsion RCW Breast Cancer Study: Protocol 102-08-201

Celsion Main Eligibility Criteria

- Patient currently has recurrent chest wall breast cancer
- Patient's superficial lesion is not greater than 3 cm in depth
- Subjects must have exhausted other available standard treatment options, including:
  - Mastectomy with standard adjuvant radiation, and/or adjuvant chemotherapy, and/or hormonal therapy
  - Chest wall radiation for non-resectable recurrent chest wall disease
  - At least two conventional systemic chemotherapy regimens for recurrent disease such as capecitabine, taxane, or anthracycline
  - If HER2+, then treatment with trastuzumab and lapatinib
  - If ER+ (or PR+), then at least one hormonal therapy in the metastatic setting
- Washout period for other systemic treatments = 28 days
- Patient has not had more than 450 mg/m2 of doxorubicin or 900 mg/m2 epirubicin
- Subjects who have previously received hyperthermia in conjunction with either radiation therapy or chemotherapy are eligible
- Patient has an ejection fraction greater than 50%

More information and details in the upcoming hyperthermia session...

Thanks for your attention!