Non-Anthracycline Adjuvant Therapy: When to Use?

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SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR NEGATIVE - HER2 NEGATIVE DISEASE

- Tumor ≤ 0.5 cm or Microinvasive
  - pN0 → No adjuvant therapy
  - pN1mi → Consider adjuvant chemotherapy

- Tumor 0.6-1.0 cm
  - Consider adjuvant chemotherapy

- Tumor > 1 cm
  - Adjuvant chemotherapy (category 1)

Histology:
- Ductal
- Lobular
- Mixed
- Metaplastic

Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)
- Adjuvant chemotherapy (category 1)

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See Follow-Up (BINV-16)

See Adjuvant Chemotherapy (BINV-K)

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See Principles of HER2 Testing (BINV-A).

Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

There are limited data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
ADJUVANT CHEMOTHERAPY1,2,3,4,5

Non-trastuzumab Containing Regimens (all Category 1)

Preferred Adjuvant Regimens:
- TAC (docetaxel/doxorubicin/cyclophosphamide)
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other Adjuvant Regimens:
- AC (doxorubicin/cyclophosphamide)
- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)
- FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- EC (epirubicin/cyclophosphamide)
- A followed by T followed by C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 weekly regimen with filgrastim support
- FEC followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) or (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)

Trastuzumab Containing Regimens (all Category 1)

Preferred Adjuvant Regimens:
- AC followed by T + concurrent trastuzumab (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
- TCH (docetaxel, carboplatin, trastuzumab)

Other Adjuvant Regimens:
- Docetaxel + trastuzumab followed by FEC (fluorouracil/epirubicin/cyclophosphamide)
- Chemotherapy followed by trastuzumab sequentially
- AC followed by docetaxel + trastuzumab

Neoadjuvant only:
- T + trastuzumab followed by CEF + trastuzumab (paclitaxel plus trastuzumab followed by cyclophosphamide/epirubicin/fluorouracil plus trastuzumab)

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

1Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2 positive tumors.
2In patients with HER2-positive and axillary lymph node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy. (category 1) Trastuzumab should also be considered for patients with HER2 positive lymph node-negative tumors greater than or equal to 1 cm. (category 1) Trastuzumab may be given beginning either concurrent with paclitaxel as part of the AC followed by paclitaxel regimen, or alternatively after the completion of chemotherapy. Trastuzumab should not be given concurrent with an anthracycline because of cardiac toxicity, except as part of the neoadjuvant trastuzumab with paclitaxel followed by CEF regimen. Trastuzumab should be given for one year, with the exception of the docetaxel + trastuzumab followed by FEC regimen in which trastuzumab is given for 9 weeks), with cardiac monitoring, and by either the weekly or every-three-week schedule.
3CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.
4Chemotherapy and tamoxifen used as adjuvant therapy should be given sequentially with tamoxifen following chemotherapy.
5Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

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Overview of Anthracycline-Induced Cardiotoxicity

- Factors which may increase the risk of cardiotoxicity:
  - Age of $\leq 4$ or $\geq 70$ years
  - Mediastinal radiotherapy
  - Pre-existing heart disease
  - Other cardiac risk factor
  - Other drugs may or may not have an additive/synergistic effect (cyclophosphamide)
Doxorubicin-Related Congestive Heart Failure

From Swain et al, (Studies 88001, 88002, 88006) 614 patients—33 cases of CHF.
From Von Hoff et al, 1979, 3,841 patients—88 cases of CHF.
## Time to Heart Failure: Patients Aged 66-70 Years

**SEER MEDICARE**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3 Years</th>
<th>5 Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline, N = 898</td>
<td>0.92</td>
<td>0.85</td>
<td>0.61</td>
</tr>
<tr>
<td>Non-Anthracycline, N = 1008</td>
<td>0.94</td>
<td>0.88</td>
<td>0.74</td>
</tr>
<tr>
<td>No Chemotherapy, N = 6939</td>
<td>0.94</td>
<td>0.88</td>
<td>0.73</td>
</tr>
</tbody>
</table>

The graph illustrates the proportion free of heart failure over time for patients aged 66-70 years, categorized by the type of chemotherapy received: adjuvant anthracycline, non-anthracycline, and no adjuvant chemotherapy. The data shows a decreasing trend in the proportion of patients free of heart failure over time, with the anthracycline group having the lowest proportion at 3 years, followed by the non-anthracycline and no chemotherapy groups. The 10-year proportion free of heart failure is also shown for each group.
The Tip of the Iceberg
Symptomatic ‘CHF’ Represents the Extreme of Heart Failure
ANTHRACYCLINES AND TAXANES ARE COMMONLY USED

• USED IN MOST REGIMENS
• LEVEL I EVIDENCE IN TRIALS AROUND THE WORLD
• OXFORD OVERVIEW CONFIRMS THE VALUE OF BOTH
EBCTCG and Anthracyclines

**Recurrence**

<table>
<thead>
<tr>
<th>Year</th>
<th>CMF</th>
<th>Anthracyclines</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>33.6</td>
<td>33.6</td>
</tr>
<tr>
<td>5-9</td>
<td>31.0</td>
<td>31.0</td>
</tr>
<tr>
<td>10+</td>
<td>45.0%</td>
<td>41.6% Anthr.</td>
</tr>
</tbody>
</table>

10-y gain 3.4% (SE 1.2)

Logrank 2p = 0.0002

**Breast Cancer Mortality**

<table>
<thead>
<tr>
<th>Year</th>
<th>CMF</th>
<th>Anthracyclines</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>22.5</td>
<td>22.5</td>
</tr>
<tr>
<td>5-9</td>
<td>19.2</td>
<td>19.2</td>
</tr>
<tr>
<td>10+</td>
<td>35.1%</td>
<td>30.8% Anthr.</td>
</tr>
</tbody>
</table>

10-y gain 4.3% (SE 1.1)

Logrank 2p < 0.00001

**Death Rate**

<table>
<thead>
<tr>
<th>Year</th>
<th>CMF</th>
<th>Anthracyclines</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>4.25</td>
<td>4.25</td>
</tr>
<tr>
<td>5-9</td>
<td>3.33</td>
<td>3.33</td>
</tr>
<tr>
<td>10+</td>
<td>2.25</td>
<td>2.25</td>
</tr>
</tbody>
</table>

Death rate: total rate - rate in women without recurrence & logrank analyses
CONCLUSIONS

• Overview shows the benefit BUT....... 
• Benefit is small 
• Consistent with only a small fraction of patients actually benefiting from anthracyclines rather than all invasive breast cancer (and this appears to be restricted to the HER2+ group)
THE TWO
NON-ANTHRACYCLINE ALTERNATIVES

- TC
- TCH
US Oncology 9735: Study Design

Eligibility: Stage I, II, or III disease
Median follow up: 5.5 years

- N=1016
- 71% ER+
- 48% N−

Chemotherapy doses based on actual BSA (no cap)
Chemotherapy given prior to radiation
Tamoxifen for all ER+ patients after chemotherapy +/- radiation
USO 9735: Effectiveness of TC Over AC

Single study—robust outcome

Worked in 65+ years (subset analysis)

### Adjuvant Trastuzumumab Options

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31</td>
<td>H...x 52</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines</td>
</tr>
<tr>
<td></td>
<td>Adjuvant Trastuzumab</td>
</tr>
<tr>
<td>NCCTG 9831</td>
<td>H...x 52</td>
</tr>
<tr>
<td></td>
<td>Epirubicin</td>
</tr>
<tr>
<td></td>
<td>Vinorelbine</td>
</tr>
<tr>
<td></td>
<td>Fluorouracil</td>
</tr>
<tr>
<td>HERA</td>
<td>No therapy</td>
</tr>
<tr>
<td></td>
<td>H...x 1 year</td>
</tr>
<tr>
<td></td>
<td>H...x 2 years</td>
</tr>
<tr>
<td>FinHer</td>
<td>H...x 9</td>
</tr>
<tr>
<td></td>
<td>H...x 9</td>
</tr>
<tr>
<td>PACS 04</td>
<td>H...x 52</td>
</tr>
<tr>
<td></td>
<td>No therapy</td>
</tr>
</tbody>
</table>

BCIRG 006

4 x AC
60/600 mg/m²

4 x T
100 mg/m²

HER2+
(central FISH*)

N+ or high-risk N-

N = 3222

AC ➔ T

AC ➔ TH

4 x AC
60/600 mg/m²

4 x T
100 mg/m²

TCH

6 x T and C
75 mg/m²

AUC** 6

Stratified by nodes and hormonal receptor status

* FISH: fluorescence in situ hybridization
** AUC: area under the concentration vs. time curve
BCIRG 006: DFS and OS (3rd Planned Analysis; 65 mo Follow-up)

Disease-Free Survival – 3rd Planned Analysis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→T</td>
<td>1073</td>
<td>257</td>
<td>1</td>
</tr>
<tr>
<td>AC→TH</td>
<td>1074</td>
<td>185</td>
<td>0.64 (0.53-0.78)</td>
</tr>
<tr>
<td>TCH</td>
<td>1075</td>
<td>214</td>
<td>0.75 (0.63-0.90)</td>
</tr>
</tbody>
</table>

Overall Survival – 3rd Planned Analysis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→T</td>
<td>1073</td>
<td>141</td>
<td>1</td>
</tr>
<tr>
<td>AC→TH</td>
<td>1074</td>
<td>94</td>
<td>0.63 (0.48-0.81)</td>
</tr>
<tr>
<td>TCH</td>
<td>1075</td>
<td>113</td>
<td>0.77 (0.60-0.99)</td>
</tr>
</tbody>
</table>

**SUMMARY OF EVENTS TCH v. ACTH**  
(BCIRG 006)  

<table>
<thead>
<tr>
<th>Event</th>
<th>ACTH</th>
<th>TCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS EVENTS</td>
<td>146</td>
<td>149</td>
</tr>
<tr>
<td>No. CHF</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>No. LEUKEMIA (myelodysplasia)</td>
<td>1</td>
<td>0(1)</td>
</tr>
<tr>
<td>TOTALS</td>
<td>168</td>
<td>153 (154)</td>
</tr>
</tbody>
</table>
WHAT DO ANTHRACYCLINES DO FOR YOU?

• Significant cardiac toxicity, some of it appearing late
• Increased nausea and vomiting, some delayed
• Rare, but real, risk of leukemia or MDS
Do we need to continue to treat patients with Anthracyclines?

Who Benefits from Anthracyclines?

- Her2neu *amplified* tumors benefit from anthracyclines
- TOP2A *amplified* patients benefit from anthracyclines
TOP2a GENE EXPRESSION

- Measured gene overexpression or deletion by FISH in over 5000 cases from BCIRG 006 and 005*

- Found overexpression to occur **ONLY** in HER 2+ cases (1/3 of cases) and in **NONE** of 2000+ cases of HER2 normal breast cancer

- Single lab with excellent quality control of testing

Topoisomerase II and Anthracycline Benefit

BCIRG 006 (HER2+)

- **Topo IIα not co-amplified**
  - Topo II amplified: Anthracycline = trastuzumab
  - Topo II negative: Trastuzumab best
  - Similar effect not seen in NSABP B-31

- **BCIRG 006 (AC-T vs. AC-TH vs. TCH) – YES**
  - Topo II amplified: Anthracycline = trastuzumab
  - Topo II negative: Trastuzumab best
  - Similar effect not seen in NSABP B-31

Changes in adjuvant breast cancer chemotherapy regimens over time in the community. Patt D et al: ASCO abstract 6109, 2012
HER2(-) and Stage I at Diagnosis

% Patients Receiving Chemotherapy

- # Pts - Recv Chemo
- TC
- AC/FAC/FEC - Paclitaxel*
- Other
- TAC
- Clinical Trial
- AC/FAC/FEC*
- AC/FAC/FEC - Docetaxel

* Includes Dose Dense
US Oncology 06-090

Node-Positive, High Risk Node Negative, HER2 Negative Breast Cancer

STRATIFICATION
  • Stage (IA, IIA, IIB, IIIA, IIIB, IIIC)

TC x 6
TAC x 6

Accrual goal - 2000 patients
DFS - Primary endpoint
Study stopped at 1200 pts.
B-46l Accrual closure and rebirth as B-49
B-49 (CTEP)

N=1843 (4200 with B-46l and TicTacToe);
Median 4+ yr IDFS;
80% Power for Non-Inferiority (HR <1.18)
Accrual opened 4/4/2012
ANTHRACYCLINES

- Very small benefit to use of anthracyclines and this benefit is almost entirely in the HER2+ population

- The predominant target of anthracyclines is TOP2a and that is found in HER2+ disease

- TC and TCH represent real world options for most patients

- Results from “the anthracycline question” trials should finally settle the debate