



EARLY STAGE BREAST CANCER

ADJUVANT CHEMOTHERAPY

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EARLY BREAST CANCER – ADJUVANT CHEMOTHERAPY

- **SUSTANTIVE DIFFICULTIES FOR A WORLDWIDE APPLICABILITY DUE TO IMPORTANT INEQUALITIES**
 - + IN DIFFERENT COUNTRIES.**
 - + WITHIN THE SAME COUNTRY**
- **GOVERNMENTAL POLITICS THAT PROVIDE ECONOMIC SUPPORT FOR HEALTH CARE SYSTEMS SHOULD BE IMPLEMENTD TO SOLVE THESE DISPARITIES THAT INFLUENCE BREAST CANCER CARE.**

FACTORS ARGUING FOR CHEMOTHERAPY INCLUSION

- **HISTOLOGIC GRADE 3 TUMOR.**
- **Ki 67 > 14 %.**
- **LOW HORMONE RECEPTOR STATUS : < 50 %.**
- **POSITIVE HER 2 NEU STATUS.**
- **TRIPLE NEGATIVE STATUS.**

MICROARRAYS

- WHERE MICROARRAYS ARE AVAILABLE, APPROVED GENETIC TESTING SUCH AS **ONCOTYPE DX** MAY BE USED TO SELECT CHEMOTHERAPY, IF NOT ALREADY INDICATED DUE TO HER 2 POSITIVITY OR ANY OTHER DETERMINANT, IN AN ENDOCRINE RESPONSIVE COHORT IN ORDER TO DETERMINE THE USE OF CHEMOTHERAPY IN ADDITION TO ENDOCRINE TREATMENT.
- **MAMMAPRINT** IS NOT YET RECCOMENDED DUE TO LACK OF PREDICTIVE VALUE.

LUMINAL A SUBTYPE

ER /PR POSITIVE.

HER 2 NEGATIVE

Ki 67 LOW: < 14 %

- **IS LESS RESPONSIVE TO CHEMOTHERAPY.**
- **CHEMOTHERAPY IS LESS USEFUL IN LUMINAL A.**
- **NO PREFERRED CHEMOTHERAPY REGIMEN
COULD BE DEFINED FOR LUMINAL A SUBTYPE**

LUMINAL B SUBTYPE

- **Luminal B Her 2 - :**
ER and / or PR +
HER 2 -
Ki 67 high
(Histologic Grade could substitute Ki 67 when absent)
- **Luminal B Her 2 +:**
ER and / or PR +
HER 2 overexpressed/amplified
Ki 67 any value
(Histologic Grade could substitute Ki 67 when absent)

- . **ANTHRACYCLINES AND TAXANES SHOULD BE INCLUDED IN THE CHEMOTHERAPY REGIMEN.**
- . **Anti HER 2 therapy could be included in HER 2 +**
- . **Endocrine Therapy may be indicated.**
- . **In Luminal B HER 2 + the use of Anti HER 2 therapy and HT is feasible after CT.**

ERB-B2 OVEREXPRESSION SUBTYPE

- **HER 2 overexpressed or amplified.
ER and PR absent.**
- . **Anti HER 2 therapy should be added to CT.
Trastuzumab optimal duration: 1 year.
Anthracyclines and Taxanes should be included in the CT.**
- . **Tumors of 5 mm. in diameter and bigger, should receive Anti HER 2 therapy. There is no evidence that smaller tumors do benefit.**
- . **Simultaneous administration is slightly better than sequential therapy.**
- . **Combined treatment – CT + Trastuzumab- in the Adjuvant setting seems better than exclusive Anti HER 2 therapy.**

BASAL LIKE SUBTYPE

- **Triple Negative: ER and PR absent
HER 2 –**

**Valid for Triple Negative and Basal Like Br. Ca.(Ductal)
Other special TN histologic subtypes are excluded.**

- . **CT: Anthracyclines, Taxanes and Alkilating agents – usually CTX – should be combined.**
- . **Antiangiogenic therapy is not included yet.**
- . **Mutated BRCA 1 – 2 carriers TN Br. Ca. are sensitive to C-DDP and Carboplatin**

SENTINEL LYMPH NODE FINDINGS.

- Prognostic value of Isolated Tumor Cells and Micrometastasis are based in:

Retrospective reviews – MIRROR -. Controversial results in different studies. Best results if Adjuvant CT is used. IHC detection has no impact in OS. ACOSOG Z0010 results, etc.: no clear and definitive recommendation for Adjuvant CT could be done.

SUGGESTION: if Isolated Tumor cells or Micrometastasis are present in the SLN, define Adjuvant CT according to the characteristics of the primary tumor (Grade, HR, HER 2 and Ki 67)

ONCOTYPE DX AND TREATMENT SELECTION

- In patients with HR +, HER 2 - , Lymph Nodes - .
- In Post-Menopausal with 1 – 3 LN + , HER 2 - , HR + .
 - RECURRENCE SCORE –RS- :
- LOW < 18: Hormone Therapy exclusive.
- INTERMEDIATE 18 - 31: CT should be discussed with each patient.
- HIGH > 31: Adjuvant CT followed by HT.

(TAILORx establish different values for RS:

LOW < 11. INTERMEDIATE 11 – 25. HIGH > 25.)

LOW RISK:

No need of Adjuvant CT. Death Risk <10%

- **T \leq 0.5 cm. HR + . HER 2 - .**
- **T 0.6 – 1 cm with absence of all these factors: G3, Lympho-vascular invasion, age < 35, HR -, HER 2 + .**
- **T 1 – 2 cm, G1 (histologic and nuclear) and absence of all these factors: Lymphovascular invasion, age < 35, HR - , HER 2 + .**
- **Patients with Lymph Node - , HR + , Oncotype Dx RS < 18.**

INTERMEDIATE RISK. Death Risk 10 – 20 %.

- **T 0.6 – 1 cm with any of these adverse prognostic factors: G3, Lymphovascular invasion, age < 35, HR - .**
- **T 1 – 2 cm, HER 2 – , with any of these adverse prognostic factors: G \geq 2, Lymphovascular invasion, age < 35 or HR - .**
- **Patients with Lymph Nodes - , HR + and Oncotype Dx with RS > 31.**

ADJUVANT CT IN INTERMEDIATE RISK.

CT COMBINATIONS WITH PROVEN EFFICACY:

- * FAC x 6
- * FEC 100 x 6
- * CAF x 6
- * CMF classic x 6 or 9.
- * CMF i/v x 6
- * TC x 4 +/- G-CSF

Age: < 50 more benefit but, also, useful in > 50.

HR < 50 % better response.

Anthracyclines increase OS but in HER 2 – less benefit.

TC additional benefit in OS over AC. Prevention of Febrile Neutropenia is required.

HIGH RISK. Risk Death > 20 %.

- **T > 1 cm . HER 2 + . (T 0.5 – 1 cm HER 2 + are considered as intermediate/high risk by several authors)**
- **Lymph Nodes + .**
- **LN – but T > 2 cm and, in particular, Triple Negative BC (ER, PR and HER 2 negatives).**
- **Patients with Lymph Nodes - , HR + and Oncotype Dx with RS > 31.**

HIGH RISK: LN + , T > 2 cm LN - , Triple Negative.

- ADJUVANT CT based in Anthracyclines and Taxanes.

TAC x 6 + Pegfilgastrim/G-CSF + Ciprofloxacin D 5-14

AC x 4 → Docetaxel x 4

FEC 100 x 3 → Docetaxel x 3

AC dose dense x 4 → Paclitaxel x 4 + G-CSF D 2-12

FEC 90 x 4 → Paclitaxel weekly x 8

AC x 4 → Paclitaxel weekly x 12

Paclitaxel weekly x 12 → AC x 4

METAANALYSIS: ADDITION OF TAXANES TO CT BASED IN ANTHRACYCLINES

13 studies with 22.903 patients evaluated.

- Recurrence Relative Risk Reduction: HR=0.83
p <0.00001
- . Recurrence of Risk Death: HR=0.85
p <0.00001

BENEFIT: is independant of

- HR expression
- LN involvement
- Taxane drug: P/D
- Menopausal status
- Sequential schedule*
- Concomitant schedule*/**

RISK REDUCTION

- **BCIRG 001** TAC vs FAC. 10 years F-up. **DFS** (Recurrence Risk reduction 20 %) and **OS** (Mortality Risk reduction 26 %)
- **GEICAM** TAC vs FAC in LN (–) but High Risk BC: **Recurrence** Risk reduction 32 %. HR=0.68, p=0,01
- **BCIRG 001 + PACS 01**: In **HR +** , recurrence risk reduction 21 %, HR=0.79. In **HR -** , reduction of 31 %, HR=0.69
- **DOCETAXEL**: benefits **HR + and HR –**
- **PACLITAXEL WEEKLY**: benefits **HR + and HR –**
- **PACLITAXEL EACH 3 w or DD**, no benefit in **HR +** (GEICAM 9906*/E1199**)
- **AC – DOCETAXEL = TAC x 6.****
- **TAC x 4 is inferior to AC – DOCETAXEL.****
- **DOSE DENSE CT Metaanalysis** of 10 studies: **DFS better** HR=0.83, p<0.005. **OS better** HR=0.85, p<0.01***

HER 2 +, T > 1 cm or LN +.

- Treatment based in CT + Trastuzumab.
- Treatment in T < 1 cm must be discussed individually if H would be included.

TCH: Doc.+ Carb.+ Herc. x 6 → H up to 1 year.

AC x 4 → TH (Taxane = Paclitaxel x 4 or 12 w. or Docetaxel x 4). H given simultaneously with the Taxane and up to 1 year.

Left ventricle ejection fraction must be monitored for H dose adjustments or suspension.

ADJUVANT TRASTUZUMAB (H) IN HIGH RISK BC.

- POSITIVE STUDIES:

+ **NASBP B-31***: ACx4→TAXOLx4 +/- H up to 1 year. **Sequential H**: DFS HR=0.67, p<0.001. OS HR=0.88, p<0.343. **Concomitant H**: DFS HR=0.65, p<0.0007**

+ **HERA*****: Any CT **Sequential H **** 1 year**: F-up 4 years. Recurrence Risk reduction 24 %. HR=0.76, p<0.0001+

+ **BCIRG 006++**: AC→T=Doc., **AC→TH, TCH. Concomitant.**

Recurr. Risk red.: AC→TH HR=0.64, p<0.001. TCH HR=0.75, p<0.04.

Death Risk red.: AC→TH HR=0.63, p<0.001. TCH HR=0.77, p<0.038++

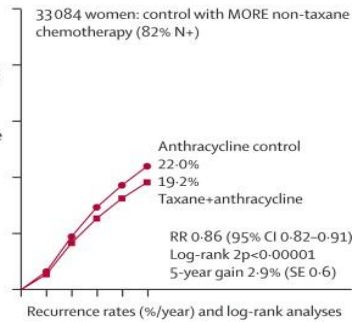
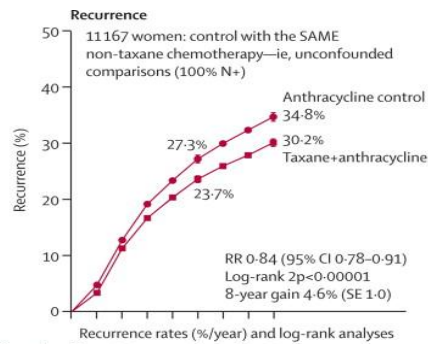
TCH < cardiotoxicity and leukemia induction.

+ **FinHer**: H 9 w. Subgroup **Concomitant Doc+H** : DF Distant Met HR=0.32, p<0.029 +++

+ **NCCTG 9831**

- NEGATIVE STUDY: PACS-04++++

* JCO 29; 4491, 2011.- ** JCO 25 Abstr 512, 2007. **** NEJM 353; 1659, 2005. + The Breast 18 (Suppl 1) abstr S25,2009.-++ NEJM 365; 1273, 2011. " ESMO Congress 2012. +++ JCO 27; 5685, 2009. ++++ JCO 27; 6129, 2009.

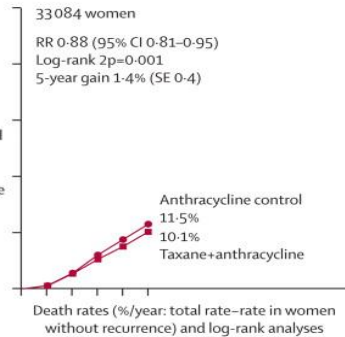
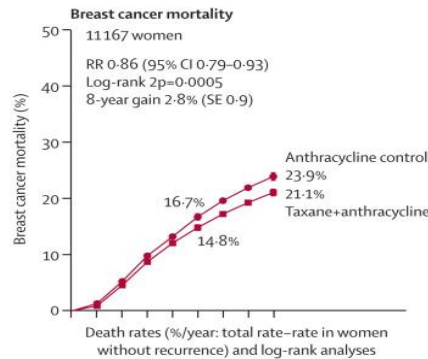


Recurrence rates (%/year) and log-rank analyses

Allocation	Years 0-4	Year 5+
Tax+anth	5.51 (1280/23249)	3.10 (413/13343)
Control	6.43 (1239/19259)	3.62 (381/10534)
Rate ratio	0.84 SE 0.04	0.85 SE 0.07
(O-E)/V	-95.5/557.3	-30.5/182.8

Recurrence rates (%/year) and log-rank analyses

Years 0-4	Year 5+
4.37 (2607/59665)	3.01 (153/5082)
5.02 (2586/51508)	2.69 (127/4727)
0.85 SE 0.03	1.03 SE 0.13
-181.4/1153.8	1.9/63.6

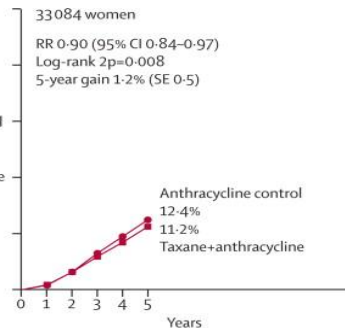
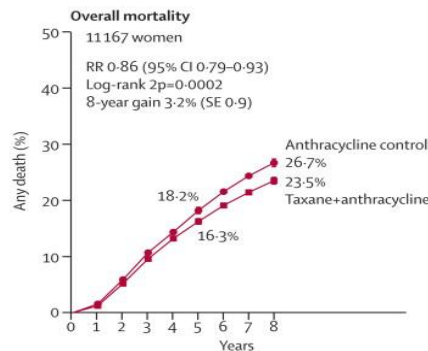


Death rates (%/year: total rate-rate in women without recurrence) and log-rank analyses

Allocation	Years 0-4	Year 5+
Tax+anth	3.21 SE 0.11	2.48 SE 0.13
Control	3.58 SE 0.13	3.06 SE 0.16
Rate ratio	0.88 SE 0.05	0.82 SE 0.07
(O-E)/V	-46.4/348.5	-33.3/172.3

Death rates (%/year: total rate-rate in women without recurrence) and log-rank analyses

Years 0-4	Year 5+
2.01 SE 0.06	2.37 SE 0.20
2.30 SE 0.07	2.26 SE 0.21
0.87 SE 0.04	0.97 SE 0.13
-77.0/549.5	-1.7/57.4



Death rates (%/year) and log-rank analyses

Allocation	Years 0-4	Year 5+
Tax+anth	3.55 (881/24821)	3.09 (465/15061)
Control	3.93 (819/20850)	3.76 (458/12178)
Rate ratio	0.88 SE 0.05	0.82 SE 0.06
(O-E)/V	-48.6/386.0	-41.3/213.4

Death rates (%/year) and log-rank analyses

Years 0-4	Year 5+
2.24 (1326/59104)	2.85 (161/5658)
2.51 (1326/52888)	2.84 (152/5358)
0.90 SE 0.04	0.96 SE 0.12
-66.3/608.4	-3.1/70.9