Anthracyclines for Breast Cancer? Are Adjuvant Anthracyclines Dispensable? Needs to be Answered in a Large Prospective Trial...

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Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

- Anthracyclines reduced risk of recurrence by 11%
- Reduced risk of death by 16%
- Absolute difference: 3% at 5 years and 4% at 10 years

Lancet 2005; 365: 1687–1717

But at what cost?

- CHF within 5 years of treatment: 0.5-1.5%
- Sub-clinical cardiac dysfunction: 10-15%
- Leukemia and myelodysplasia within 5-10 years: 0.4-1.7%

Two Studies:

- AC versus TC: Jones et al 2007 and 2009
- BCIRG 006: Her2 + SABCS 2009

Disease Free Survival

Overall Survival

Limitations:
- Is AC x 4 the best comparator?
- Is duration of treatment important: Is longer better? NSABP B30:
- OS: AC-Docetaxel (8 cycles): 8 yr OS 83% compared with AT 79%, HR 0.83; P=0.03, compared with TAC x 4 79%, HR 0.86, P =0.09


TC versus TAC: USOR 06090/NSABP B46-I/07132
- TC x 6 versus TAC x 6 in Her2 negative Early Stage Breast Cancer
- Original goal: 2000 pts (superiority)
- Combined forces with the NSABP to add third arm: TC with Bevacizumab...3900 pts
- Drop in enrollment with uncertainty about Bevacizumab
- Return to the original TC versus TAC question (total of 3500 pts), non-inferiority
- Tissue obtained on first 2000...
- "Stay Tuned…"

Can we Define a Group of Patients who Might Benefit from Anthracyclines: Her2 positive

Gennari, AJNCI 2008; 100:14-20

Can We Omit Anthracyclines in Her2+ BC?

Slamon D, SABCS 2009, abstract 62
- Can we Define a Group of Patients who Might Benefit from Anthracyclines:

BCIRG 006
- Overall Survival – 3rd Planned Analysis

HER2 and TOPO IIa in BCIRG 006
- 2900 of 3222 patients tested

Topo II

Non Co-Amplified

Co-Amplified
Considerations in Anthracycline Efficacy


Conclusions from MA 5

- CEF > CMF
  - Her2 Positive
  - TOP2A Amplified or Deleted
topo2α. Overexpressed
  - But amplification at DNA level doesn’t correlate with protein expression

Effects of Doxorubicin on Topoisomerase 2A

- Doxorubicin binds to DNA, blocking the progression of TOPO 2α which unwinds DNA for transcription
- Doxorubicin stabilizes the TOPO 2α complex after it has broken the DNA chain for replication
- Doxorubicin prevents the DNA double helix from being resealed, interrupting the process of replication
- Action of Doxorubicin is dependent on the amount of TOPO 2α in the cell

Correlation Between TOP2A Expression and Response to Doxorubicin and Docetaxel: Pre-operative Treatment with Either Dox 75 mg/m2 x 4 or Doc 100 mg/m2 x 4: 204 pts

- Predictors of sensitivity to Dox: low TOP2A expression, ER-
- Predictors of sensitivity to Doc: small size and ER+
- Triple Negative: resistance to Dox...

TOP2A Overexpression: Prognostic Information: 1681 Breast Tumors


TOP2A Expression and Risk of Recurrence

- Sparano et al: E2197 AC vs AT
- Expression by RT PCR
- Overall: AC or AT, no difference in recurrence
- However, in HR + Her2-, TOP2A expression was associated with increased risk of recurrence: p = 0.01
- This was complimentary to RS
- Trend to better outcome with AT if high TOP2A expression


TOP2A: 782 pts with Node Neg BC, No Adjuvant Therapy
and 80 pts treated with neo-adjuvant EC

Neoadjuvant Trial of Principle: TOP Trial

- Goal: To identify molecular markers that predict response/resistance to anthracyclines
- ER negative pts treated with Epirubicin
- 139 evaluable for response prediction analysis
- Primary Endpoint: pCR: 14%
- TOP2A gene amplification but not protein expression: associated with pCR in the Her2+ pts and with pCR in Her+/ER- pts (additional validation series)


So What to Make of TOP2A?

- High TOP2A expression and high topo2α protein: benefit of anthracyclines
- But what about triple negative… if too much topo2α, can overcome effect of anthracyclines
- ER+, TOP2A high, poor prognosis
- What is the optimal way to study? Protein by IHC or RNA expression?
- Can we use this yet to identify sub-types who require anthracyclines?
- Hope to answer with the TC/TAC adjuvant trial…

So are we ready to abandon Anthracyclines?

- Not yet
- TC/TAC should be definitive
- Look to subsets to help clarify
- Need large numbers of high risk patients with aggressive biology to answer