5 Minute JournalClub

Key SABCS Presentations

Issue 7, 2011

Effect of Number of Treatment Cycles of Adjuvant Chemotherapy on Clinical Outcomes

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVE

- Apply the results of new research to your recommended total duration of adjuvant chemotherapy for patients with early breast cancer and zero to three positive axillary nodes.

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This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Novartis Pharmaceuticals Corporation and Sanofi-Aventis.

Last review date: March 2011
Expiration date: March 2012

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Click here for SABCS papers on HER2-negative breast cancer

In 2001 the first results from the ATAC trial demonstrated the superiority of an AI (anastrozole) over tamoxifen. One year later a CALGB study showed an advantage for dose-dense AC→paclitaxel, and not long after that US Oncology proved that TC was better than AC and along the way the NSABP presented data on the Onco*type* DX® assay to help select patients for adjuvant chemo. However, since the presentation of those important yet modest research advances, one could make the argument that not a whole lot else positive has happened in adjuvant treatment for the 80 percent of patients with HER2-negative breast cancer.

2010 didn't do much to change this situation — at least that's my conclusion after watching Alan Coates' San Antonio "Year in Review" presentation on the management of early breast cancer. Of the 18 papers he discussed during this talk, none seem likely to lead to a meaningful change in the mortality of this disease. Perhaps the most provocative of the bunch highlighted by Dr Coates were the three neoadjuvant HER2-positive papers reviewed in a previous issue of this series. However, the HER2-negative papers that were "featured" made me long for a myeloma-like infusion of new agents that actually work.

Unfortunately, it's not totally clear that this is on the horizon, especially if the data sets coming out in San Antonio are any indication. What we saw there were mainly a few legacy studies evaluating adjuvant chemotherapy, including:

1. Findings from another **CALGB trial** suggesting similar outcomes with four and six cycles of dose-dense paclitaxel or AC.

2. **Two trials** testing the addition of capecitabine to anthracycline/taxane regimens demonstrating questionable or no benefit, although **two other** related data sets suggested a slightly greater advantage with cape in triple-negative disease.

3. Early **tolerability data** on "maintenance" capecitabine after an anthracycline and/or a taxane — a strategy that makes sense, but no definitive efficacy data exist yet.

4. Another **early safety report** in a trial evaluating bevacizumab/chemotherapy in the adjuvant setting, but the recent negative results of two adjuvant trials of bev in colon cancer have perhaps dampened enthusiasm for this approach.

It's a real disconnect to walk through the halls of San Antonio and see thousands of investigators presenting a seemingly endless array of data sets and still contemplate the fact that the current overall impact of this effort at a patient care level — especially in the most prevalent HER2-negative breast cancer subset — is relatively modest. It makes one wonder if we will soon see the payoff of this extensive investment in research and whether there is any way to change the trajectory of progress.

Next up on our final San Antonio issue of *5-Minute Journal Club*: Clinical trials in metastatic disease, including studies of combinations of biologic agents

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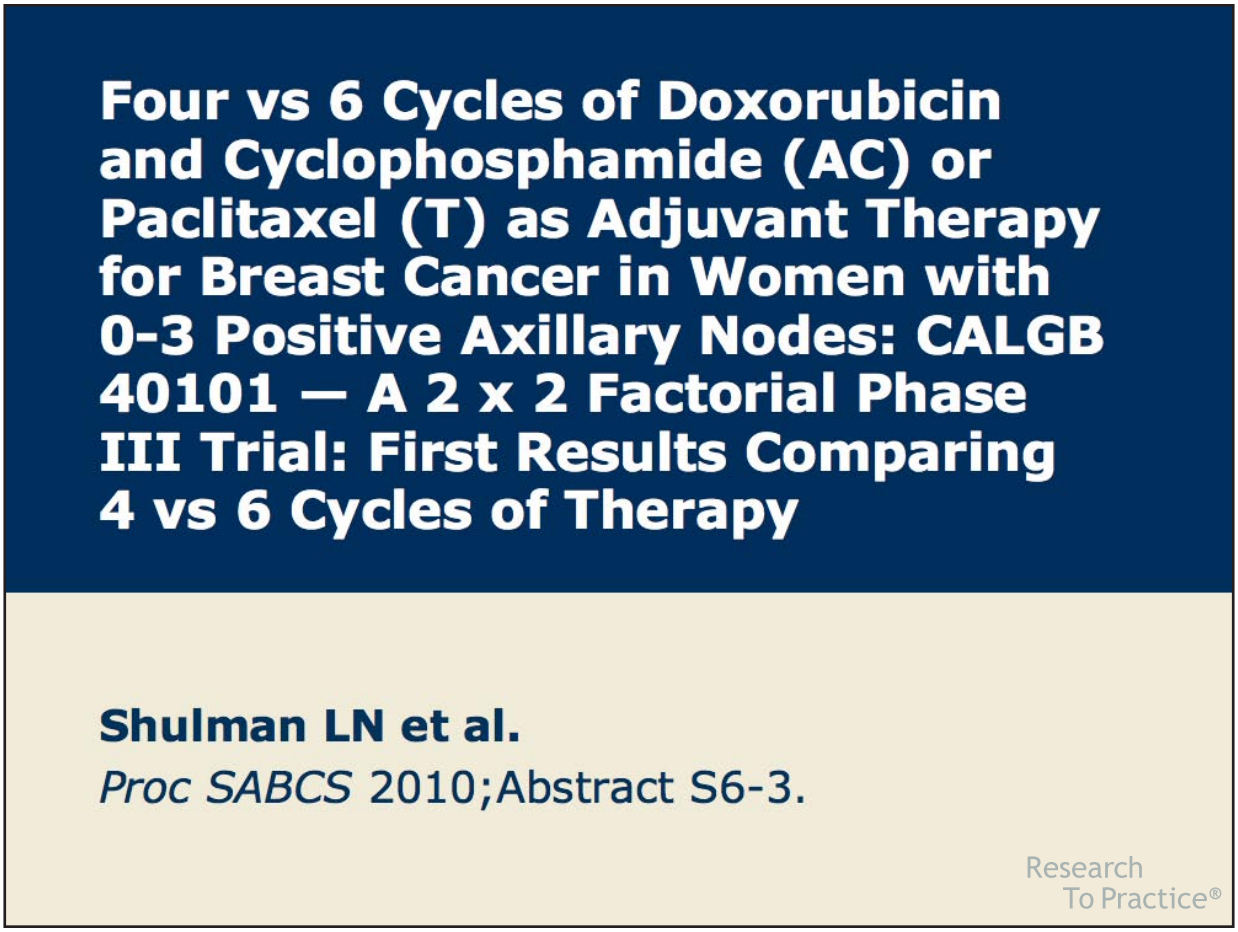
Effect of Number of Treatment Cycles of Adjuvant Chemotherapy on Clinical Outcomes

Presentation discussed in this issue

Shulman LN et al. **Four vs 6 cycles of doxorubicin and cyclophosphamide (AC) or paclitaxel (T) as adjuvant therapy for breast cancer in women with 0-3 positive axillary nodes: CALGB 40101 — A 2x2 factorial phase III trial: First results comparing 4 vs 6 cycles of therapy.** San Antonio Breast Cancer Symposium 2010;**Abstract S6-3**.

Slides from a presentation at SABCS 2010 and transcribed comments from a recent interview with William J Gradishar, MD (1/4/11)



Study Objectives

- **Primary Objectives**
  - Determine the equivalence of T with AC for relapse-free survival (RFS)
  - Determine if longer therapy (6 cycles) is superior to shorter therapy (4 cycles), regardless of agent, regarding RFS
- **Secondary Objectives**
  - Overall survival (OS)
  - Toxicities
  - Impact of 6 cycles versus 4 cycles in regard to induction of menopause in premenopausal women
  - Quality of life

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

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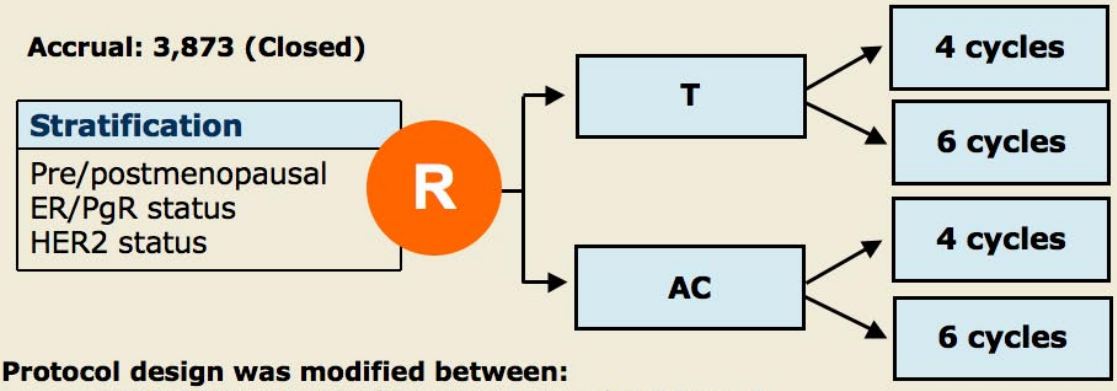
CALGB-40101: Study Design



Protocol design was modified between:

- 2002-2003: AC q 3 wks x 4 or 6, T q wk x 12 or 18
- 2003-2008: AC q 2 wks x 4 or 6, T q 2 wks x 4 or 6
- 2008-2010: AC q 2 wks x 4, T q 2 wks x 4

Current analysis:

- 4 versus 6 cycles of therapy
- Data on AC versus T not yet released by Data and Safety Monitoring Board

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

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Efficacy Data and Select Grade 3 and 4 Adverse Events

Median follow-up: 4.6 years

Number of Cycles	4-Year RFS	Hazard Ratio	*p*-value
4 cycles 6 cycles	91.8% 91.6%	1.10	0.420
Number of Cycles	**4-Year OS**	**Hazard Ratio**	***p*-value**
4 cycles 6 cycles	96.4% 95.3%	1.31	0.097

Toxicity	AC x 4 (n = 796)	AC x 6 (n = 790)	T x 4 (n = 798)	T x 6 (n = 789)
Neutropenia	26%	34%	3%	3%
Neuropathy	0%	0%	6%	13%
Anemia	2%	6%	0%	1%

There were 10 patients with Grades 3 to 5 cardiac events, but the percent is <1%

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

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AML/MDS

- A total of 6 patients developed AML or MDS that was diagnosed 11-27 months after AC therapy:
  - AML: 5 patients
  - MDS: 1 patient
- Five patients developed AML/MDS in the AC x 6 study arm.
- One patient developed AML/MDS in the AC x 4 study arm.
- Five patients have died (including the one patient with MDS).
- No cases of AML/MDS were observed among the patients who received paclitaxel.

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

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Author Conclusions

- Six cycles of AC or T for patients with primary breast cancer and 0 to 3 positive axillary nodes is not superior to 4 cycles of therapy.
- Although there are only 288 RFS events to this point, based on the present data, the Bayesian predictive probability of concluding superiority of 6 cycles (a primary goal of the study) with 567 RFS events is only 0.001.
- No interaction was evident between these findings and ER or HER2 status or whether the patient received AC or T (data not shown).

Shulman LN et al. *Proc SABCS* 2010;Abstract S6-3.

Investigator Commentary: Number of Cycles of Chemotherapy for Early Breast Cancer

CALGB-40101 was modified many times since it was opened in 2002, but in essence the study demonstrated that more cycles of adjuvant chemotherapy — whether it's six cycles of AC or paclitaxel — is not better than four cycles of the same chemotherapy. This was true for patients with ER-positive and ER-negative breast cancer. The statisticians are confident that this result will not change with more follow-up and a greater number of events. In short, more cycles of adjuvant chemotherapy does not make a difference in patient outcomes.

Interview with William J Gradishar, MD, January 4, 2011

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