5 Minute JournalClub

Cardiac Safety Results of a Docetaxel/Cyclophosphamide/ Trastuzumab Combination in Patients with HER2-Positive Early-Stage Breast Cancer

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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 where 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

- Identify the cardiac safety of the combined regimen of docetaxel, cyclophosphamide and trastuzumab when administered in the adjuvant setting to patients with HER2-positive early-stage breast cancer.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Mark D Pegram, MD
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IN THIS ISSUE:

Shortly before the recent Pro Bowl in Miami, our CME group hosted a marquee event of our own about ten minutes from the stadium as nine breast cancer "all stars" came together in our sound studio for a daylong think tank audio recording. It's not surprising that my mental highlight film from the meeting includes many innovative ideas and poignant comments by the soft-spoken and super-smart Harvard maven, Dr Paul Goss.

In a follow-up audio interview with Paul, he thoughtfully discussed several patients from his practice. The case that stood out for me was a 38-year-old woman who came for a second opinion after having received several different chemo/anti-HER2 regimens for metastatic disease. This patient's original primary tumor was ER-positive, HER2-positive, but on recurrence a vertebral biopsy revealed HER2-positive, ER-*negative disease*, and she had not received endocrine therapy since the disease recurred.

According to Paul, at this point the woman was sick and tired of being sick and tired of chemo, which in part prompted his highly interesting and somewhat unusual treatment recommendation of the combination of letrozole, trastuzumab and lapatinib, an innovative biologic triplet that makes a lot more sense since Kim Blackwell's stunning **San Antonio presentation** profiled in our slide set, which compared lapatinib to trastuzumab/lapatinib in patients with heavily pretreated metastatic disease. Her presentation was an update of the data that were just published in the *Journal of Clinical Oncology*.

Listening to Paul's case, I was particularly interested in his explanation for using endocrine therapy in spite of a recent ER-negative biopsy, which was based on his concern about the possibility of sampling error particularly because the tissue biopsied was bone, which he feels is ripe for inaccuracies. An equally important factor in his recommendation is the relative lack of toxicity with hormone therapy and the recent data supporting the addition of anti-HER2 therapy to up-front endocrine treatment of metastatic disease. Paul and others believe that anti-HER2 treatment may potentiate

endocrine therapy by a variety of mechanisms including interference with ligand-independent ER activation.

In terms of the HER2 part of this interesting triplet, Paul, like most San Antonio attendees, was very impressed with the trastuzumab/lapatinib data set — one of the very few recent trials to demonstrate a survival benefit in metastatic disease in spite of a built-in crossover design. Dr Goss believes part of the explanation for this finding is that these patients had received so many prior therapies that post-trial intervention had less impact. Another important principle borne out by this study is the potential benefit of continuing trastuzumab beyond disease progression, which was previously supported by the German trial of trastuzumab/capecitabine in patients with disease progression on trastuzumab with other chemo agents. During the think tank, the faculty commented on the sea change in approach to patients with metastatic HER2-positive disease that resulted from this study and the trastuzumab/lapatinib trial in which continuous anti-HER2 therapy has quickly become routine clinical practice.

Although many viewed the recent Pro Bowl as a sham in which the participants seemingly could have cared less about the outcome, I smile inwardly reflecting on a pretty amazing day with Paul and our other "All Pro" investigators. The intriguing clinical and laboratory science discussed that "Super" day suggests that the biology of this disease is finally coming together in a way that maybe will soon have a meaningful impact on patient care.

Next up on 5-Minute Journal Club: San Antonio excitement on bone-targeted therapy.

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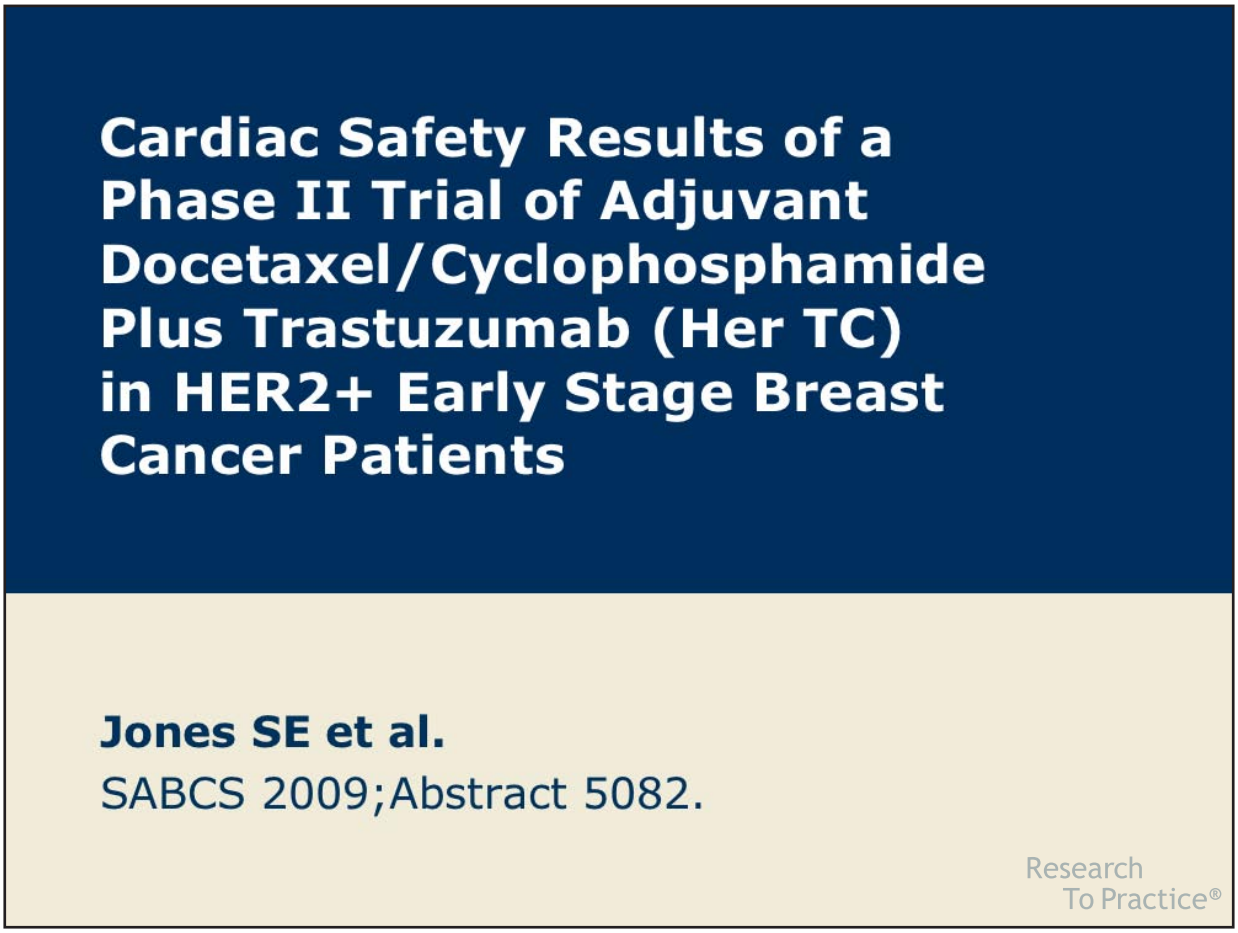
Cardiac Safety Results of a Docetaxel/Cyclophosphamide/ Trastuzumab Combination in Patients with HER2-Positive Early-Stage Breast Cancer

Presentation discussed in this issue

Jones SE et al. **Cardiac safety results of a Phase II trial of adjuvant docetaxel, cyclophosphamide plus trastuzumab in Her2+ early stage breast cancer patients.** San Antonio Breast Cancer Symposium 2009;**Abstract 5082**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Mark D Pegram, MD (12/23/09)



Introduction

- Phase III US Oncology Research trial 9735 demonstrated that docetaxel/cyclophosphamide (TC) was significantly superior to doxorubicin/cyclophosphamide in patients with early breast cancer (BC) in the adjuvant setting (*JCO* 2009;27:1177).
  - Disease-free survival (median 7 yrs): 81% vs 75%, p=0.033
  - Overall survival: 87% vs 82%, p=0.032
- Addition of anthracycline therapy to trastuzumab treatment is associated with an increase in the risk of cardiotoxicity.
- Phase II trial demonstrated that trastuzumab combined with TC (Her TC) is a nonanthracycline-containing regimen that was well tolerated as an adjuvant therapy in patients with HER2+ early BC (SABCS 2008;Abstract 2111).
- **Current study objective:**
  - Determine the cardiac safety of Her TC in patients with HER2+ early breast cancer.

Jones SE et al. SABCS 2009;Abstract 5082.

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Phase II Trial of Her TC in Patients with HER2+ Early BC

Accrual: 263
(260 patients comprised cardiac safety population)

Eligibility
Invasive BC
T1 or T2 Tumor size
N0 or N1 Lymph node status
Her2+ (IHC 3+ or FISH+)
LVEF ≥ 50% by MUGA or ECHO

→ **Docetaxel (T)**
Cyclophosphamide (C)
Trastuzumab (H)

T = 75mg/m² IV q 3 weeks x 4
C = 600mg/m² IV q 3 weeks x 4
H = 4mg/Kg Wk 1 →
2mg/Kg/week Wk 2-12 →
6mg/Kg q 3 weeks Wk 13-52

Jones SE et al. SABCS 2009;Abstract 5082.

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Methods

- LVEF assessed at baseline and then q3 months.
- Trastuzumab held for any of the following reasons:
  - ≥15% decline in absolute LVEF from baseline
  - ≥10% decline in absolute LVEF from baseline and current LVEF ≥1% lower than lower limit of normal.
- Repeat MUGA (or ECHO) in 4 weeks for any of the following reasons:
  - Trastuzumab held for the above reason
  - LVEF >5% below lower limit of normal
- If criteria for continuation are met at repeat MUGA then trastuzumab is resumed.
- If trastuzumab held for 2 consecutive periods or for a total of 3 holds, then trastuzumab may be discontinued.

Jones SE et al. SABCS 2009;Abstract 5082.

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Treatment Outcomes (1-year follow-up)

Outcome	n (%)
Normal completion	206 (78.3)
Remains on treatment	11 (4.2)
Study discontinuations	46 (17.5)
Reason for discontinuation	
Patient request	12 (4.5)
Disease progression on study	1 (0.4)
Other	5 (1.9)
Lost to follow-up	1 (0.4)
Toxicity	27 (10.3)

Jones SE et al. SABCS 2009;Abstract 5082.

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Cardiac Events and Parameters (n = 260)

- Number of patients with cardiac toxicity leading to discontinuation: 11 (4.2%)
  - LVEF dysfunction: 9 (3.4%)
  - Brachycardia/syncope: 1 (0.4%)
  - Chest pain: 1 (0.4%)
- Number of patients with absolute ↓LVEF ≤ 50% any time during treatment: 16 (6.1%)
- Median LVEF at baseline: 64%
- Median LVEF at ≥ 10 months: 63%
- No cases of CHF were observed.

Jones SE et al. SABCS 2009;Abstract 5082.

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Conclusions

- Cardiac events are uncommon with Her TC regimen administered to patients with HER2+ early BC.
  - Sixteen patients (6.1%) experienced LVEF decline to ≤ 50% any time during treatment.
  - Nine patients (3.4%) discontinued trastuzumab due to decrease in LVEF.
  - No cases of CHF were observed.

Jones SE et al. SABCS 2009;Abstract 5082.

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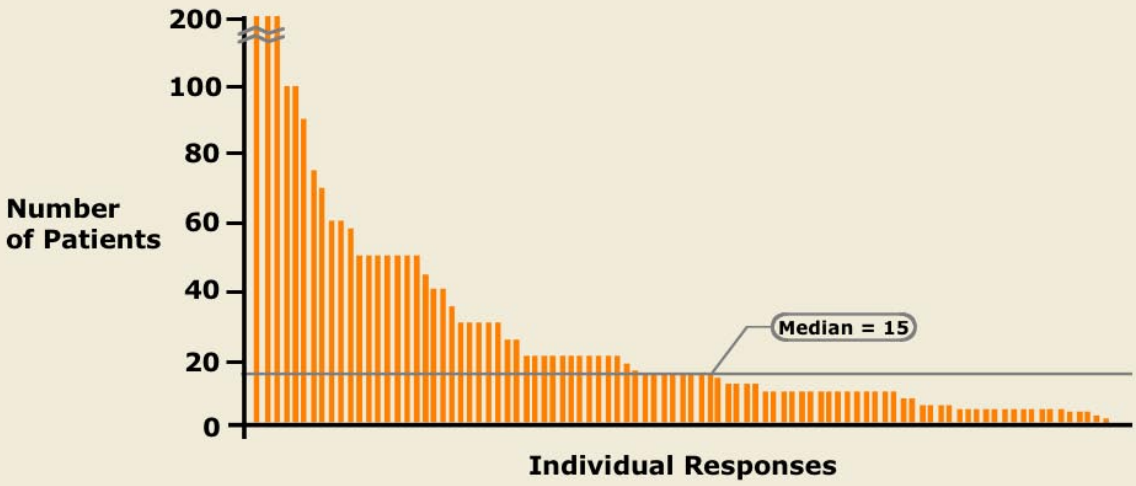
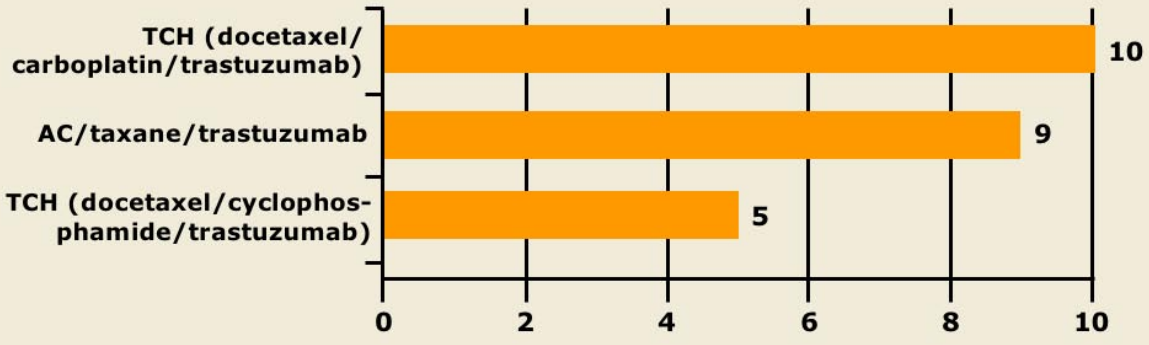
In the past year, how many patients have you treated with adjuvant trastuzumab?



Responses from 94 of 100 physicians who have treated patients with adjuvant trastuzumab in the past year.

Patterns of Care in Breast Cancer — Survey of 100 US-based Medical Oncologists.

How many patients have you treated with each of the following trastuzumab regimens in the adjuvant setting? (median)



Patterns of Care in Breast Cancer — Survey of 100 US-based Medical Oncologists.

DR PEGRAM: The docetaxel/cyclophosphamide combination is a very reasonable backbone on which to add trastuzumab. We had previously published data showing that cyclophosphamide was synergistic with trastuzumab, much the same as platinum salts are synergistic with trastuzumab in preclinical models. The scientific rationale here is sound.

Moreover, in the Phase III BCIRG 007 trial, when we evaluated docetaxel/trastuzumab with or without carboplatin, there was actually no statistically significant difference between the two arms. This suggests that carboplatin may not be the home run we had hoped it would be, and it opens the door for other agents to be studied. Cyclophosphamide is a reasonable candidate.

These data are based on 260 patients with HER2-positive breast cancer who have been followed for one year on this adjuvant study of trastuzumab combined with docetaxel/cyclophosphamide (Her TC). The median age was 55 years old.

In this trial, 27 patients, or 10.3 percent, discontinued treatment due to adverse events. Cyclophosphamide is extremely well tolerated. I can't imagine that it would be any less tolerable than carboplatin, though I don't know that it is better tolerated. Carboplatin may cause more peripheral neuropathy, which is a consideration for patients with preexisting conditions such as diabetes, and it has a greater effect on the platelet count.

I've used this Her TC regimen and I like it. I've even had the occasion to use it off study, and I believe it's reasonable to move it forward. Based on our experience with TCH, these data are about what I would expect. In the BCIRG 006 trial, it was exceedingly rare to withdraw a patient from TCH as a consequence of LVEF declines. Patients who received ACTH, however, had statistically significant drops in EF.

In terms of cardiac events, this Her TC combination looks fairly comparable to the classic docetaxel/carboplatin/trastuzumab (TCH) regimen used in the BCIRG 006 trial.

In this trial, 16 patients, or 6.1 percent, had declines of LVEF to 50 percent or less during treatment, and there were no cases of clinical congestive heart failure. In the BCIRG 006 trial, which randomly assigned over 1,000 patients to TCH, the incidence of clinical congestive heart failure was approximately 0.4 percent, so very close to zero.

We have a lot of data on the TC regimen in non-HER2-positive disease, showing that it's superior to AC, so why not use it as a base for treating HER2-positive disease? I believe that makes perfect sense. My personal philosophy is that in the grand scheme of things, I believe history will record that which chemotherapy backbone we use with HER2-targeted therapy is irrelevant. The important consideration is the integration of the HER2-targeted agent, and there are any number of combinations that I would be comfortable with, including Her TC.

Dr Pegram is Full Professor of Medicine and Director for the Translational Research Program at the Braman Family Breast Cancer Research Institute at UM Sylvester Comprehensive Cancer Center in Miami, Florida.