5 Minute JournalClub

Key SABCS Presentations
Issue 7, 2011

Safety Analysis of Bevacizumab-Containing Adjuvant Chemotherapy in a Phase II Pilot Trial

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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

- Recall the early safety findings with adjuvant docetaxel, cyclophosphamide and bevacizumab in the management of HER2-normal early-stage breast cancer.

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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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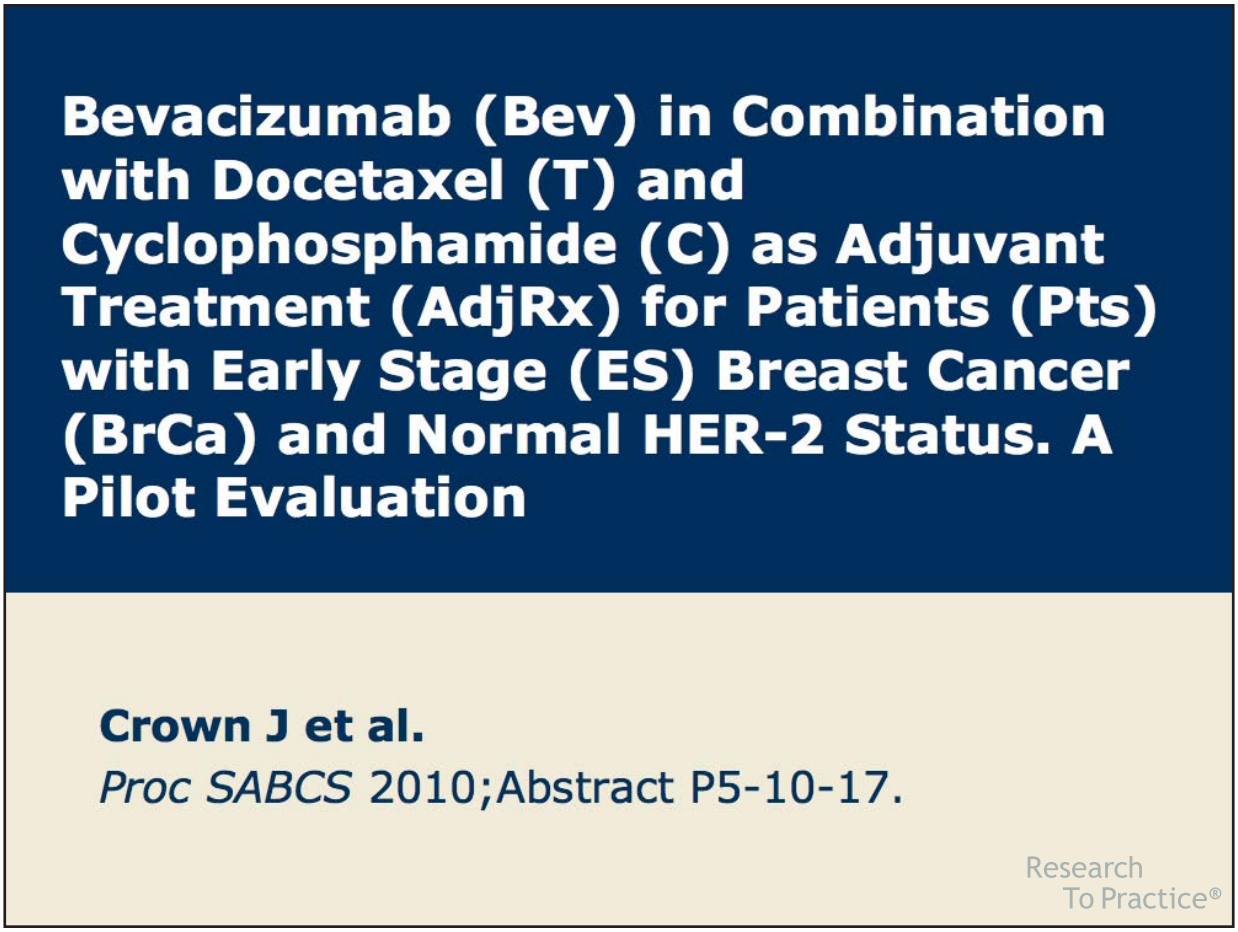
Safety Analysis of Bevacizumab-Containing Adjuvant Chemotherapy in a Phase II Pilot Trial

Presentation discussed in this issue

Crown J et al. **Bevacizumab (Bev) in combination with docetaxel (T) and cyclophosphamide (C) as adjuvant treatment (AdjRx) for patients (pts) with early stage (ES) breast cancer (BrCa) and normal HER-2 status. A pilot evaluation.** San Antonio Breast Cancer Symposium 2010;**Abstract P5-10-17**.

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



Methods

Accrual = 106 (Closed)

Eligibility
Early-stage breast cancer (ESBC) HER2-normal Node-positive, or >2 cm and receptor-negative, or >3 cm and receptor-positive Normal cardiac ejection fraction

→ Docetaxel[1]
Cyclophosphamide[2]
Bevacizumab[3]

Patients were monitored clinically, with blood pressure (BP) measurements before each bevacizumab infusion, regular echocardiograms and serial estimations of B-type natriuretic peptide (BNP) and troponin.

[1] 75 mg/m^2 day 1 q3wk x 4
[2] 600 mg/m^2 day 1 q3wk x 4
[3] 15 mg/kg day 1 q3wk x 18

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17;
ClinicalTrials.gov Identifier NCT00911716.

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Patient Disposition

	TC + Bev (n = 106)
Therapy completion (all phases)	46 (43.4%)
Still on treatment	39 (36.8%)
Removal from study	21 (19.8%)
Hypertension	6 (5.66%)
Intestinal perforation	2 (1.89%)

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17.

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Select Serious Adverse Events (SAEs)*

n (%)	TC + Bev
SAEs (all types, any grade)†	21 (19.8%)
Neutropenia	5 (4.7%)
Neutropenic sepsis	3 (2.8%)
Cellulitis	3 (2.8%)
Pyrexia	2 (1.9%)
GI perforation	2 (1.9%)

* Occurring in >1% of patients on study

† 34 SAEs (31 involved hospital admissions, 3 were serious for other reasons) occurred on study in these 21 patients

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17.

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Hypertension and Cardiac Toxicity

Hypertension (HTN)	TC + Bev (n = 106)
HTN (while on study)	**41 (39.8%)**
HTN (requiring antihypertensives)	35 (85.4%)
Time to onset of hypertension (median)	154 days

Cardiac toxicity; median ejection fraction (EF) at baseline = 67%	
Drop in EF of 10-15% from baseline	22 (21.2%)
Drop in EF of 15-20% from baseline	6 (5.8%)
Drop in EF of >20% from baseline	2 (1.9%)
Drop in EF to <50%	8 (7.7%)

No cases of congestive heart failure observed. Serial estimations of BNP and troponin indicated no significant changes throughout the study treatment.

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17.

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Author Conclusions

- The spectrum and frequency of bevacizumab toxicity in this study were similar to those reported for patients with metastatic breast cancer and other types of cancer.
- Hypertension was the principal cause of treatment discontinuation, but cardiac toxicity appeared to be limited.
- Intestinal perforation can also occur in patients with ESBC even without history of previous abdominal surgery or intestinal chronic diseases.
- These toxicities can occur in the post-chemotherapy phase of bevacizumab therapy.
- Patients enrolled on randomized trials of bevacizumab-containing adjuvant therapy require careful monitoring for toxicity.

Crown J et al. *Proc SABCS* 2010;Abstract P5-10-17.

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Investigator Commentary: Safety of Bevacizumab in Combination with Docetaxel/Cyclophosphamide in the Adjuvant Setting

This pilot study by Crown and colleagues was a small, single-arm clinical trial with approximately 100 patients. They demonstrated that it was feasible to administer bevacizumab with adjuvant docetaxel and cyclophosphamide. No surprises were observed with respect to side effects.

Some hypertension occurred, which is predictable, but no significant cardiac signal was observed. Obviously, we cannot make any comments whatsoever about efficacy, so the key data will come from the large, ongoing trials evaluating bevacizumab in the adjuvant setting.

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

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