5 Minute JournalClub

Key SABCS Presentations
Issue 5, 2011

A Prospective and Retrospective Registry of Pregnant Patients with 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 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

- Counsel patients who are diagnosed with breast cancer during pregnancy about the known benefits and risks of delivering treatment prior to or after delivery.

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No real or apparent conflicts of interest to disclose.

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Key SABCS Presentations
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Click here for key papers on endocrine/metabolic issues from the 2010 SABCS

The first targeted therapy for cancer came in the form of an innocuous-appearing pill that for many patients with ER-positive breast tumors was more efficacious than chemotherapy (CT). Thanks to mavens like Craig Jordan, we have known for quite a while that the antitumor effect of tamoxifen (TAM) comes via a metabolite (endoxifen), and thus it made sense that patients with genetic deficiencies of the activating enzyme (CYP2D6) might experience less or no treatment benefit. That being said, prior studies attempting to validate this concept have yielded conflicting results.

Related to this issue, a number of prominent TAM/investigator advocates have hypothesized that the 20 percent reduction in recurrences in trials of adjuvant AIs versus TAM wasn't the result of inherently greater antitumor efficacy but rather because a fraction of women in these studies actually had CYP2D6 deficiency. **Two major presentations** at San Antonio pretty much debunked that theory and added several more nails to the CYP2D6 coffin.

For these studies, investigators accessed available tissue from patients enrolled in two of the largest AI trials — ATAC (anastrozole) and BIG 1-98 (letrozole) — assayed for CYP2D6 genotypes and found no correlation with recurrence rate in patients receiving AIs (as would be expected) or TAM. Although investigators seem ready to abandon CYP2D6 testing in clinical practice outside a protocol setting, it is important to consider that the majority of the available data — including these two new reports — are in postmenopausal subsets. However, TAM is now most commonly used in premenopausal patients, where the hormonal environment (high estrogen levels) is very different. Vered Stearns and ECOG just opened a new trial in metastatic disease to further study this continuing story. Our recent Patterns of Care survey demonstrated that 41 percent of community oncologists have ordered a CYP2D6 assay at least once, and although that practice now seems more questionable than ever, it still makes sense to avoid inhibitors of the enzyme like SSRIs in patients receiving TAM.

We've come a long way in understanding endocrine and metabolic issues in breast cancer in the four decades since TAM first entered oncology practice, and in this issue of *5-Minute Journal Club* we peruse several other interesting related San Antonio papers.

1. **More on 500-mg fulvestrant dosing**

John Robertson presented additional data from the FIRST trial evaluating front-line fulvestrant in metastatic disease, which continues to report benefit with the increased monthly dose after loading. The current data demonstrate a median time to progression of 23.4 months for fulvestrant 500 compared to 13.1 months with anastrozole.

2. **Treatment of breast cancer during pregnancy**

This landmark European registry reported on 313 women diagnosed with breast cancer during pregnancy, including 142 who received CT while still pregnant and 118 who received it immediately after childbirth (with medians of 20 and 28 weeks of gestation, respectively, at the time of diagnosis). Breast cancer and fetal outcomes were similar in the two groups but premature delivery was more common (33 percent) in the delayed group, probably to hasten the time to receive CT. The authors concluded that oncologists should generally use CT during pregnancy rather than expose women and fetuses to the potential complications of premature delivery.

3. **Three papers demonstrating the negative prognostic impact of obesity in the adjuvant setting**

The 2005 presentation by Rowan Chlebowski of the WINS trial demonstrated fewer breast cancer recurrences in women randomly assigned to counseling to reduce dietary fat, and this sparked a series of related analyses along with three new important data sets in San Antonio. Of particular note was an extraordinary presentation by Joe Sparano of data from several recent ECOG randomized trials demonstrating that obese (BMI > 30 kg/m^2) patients had an increased risk of recurrence independent of other factors. This general body of work continues to have important practice and translational research implications.

Next up on this San Antonio highlights series: More on the increasingly complex world of HER2-positive breast cancer.

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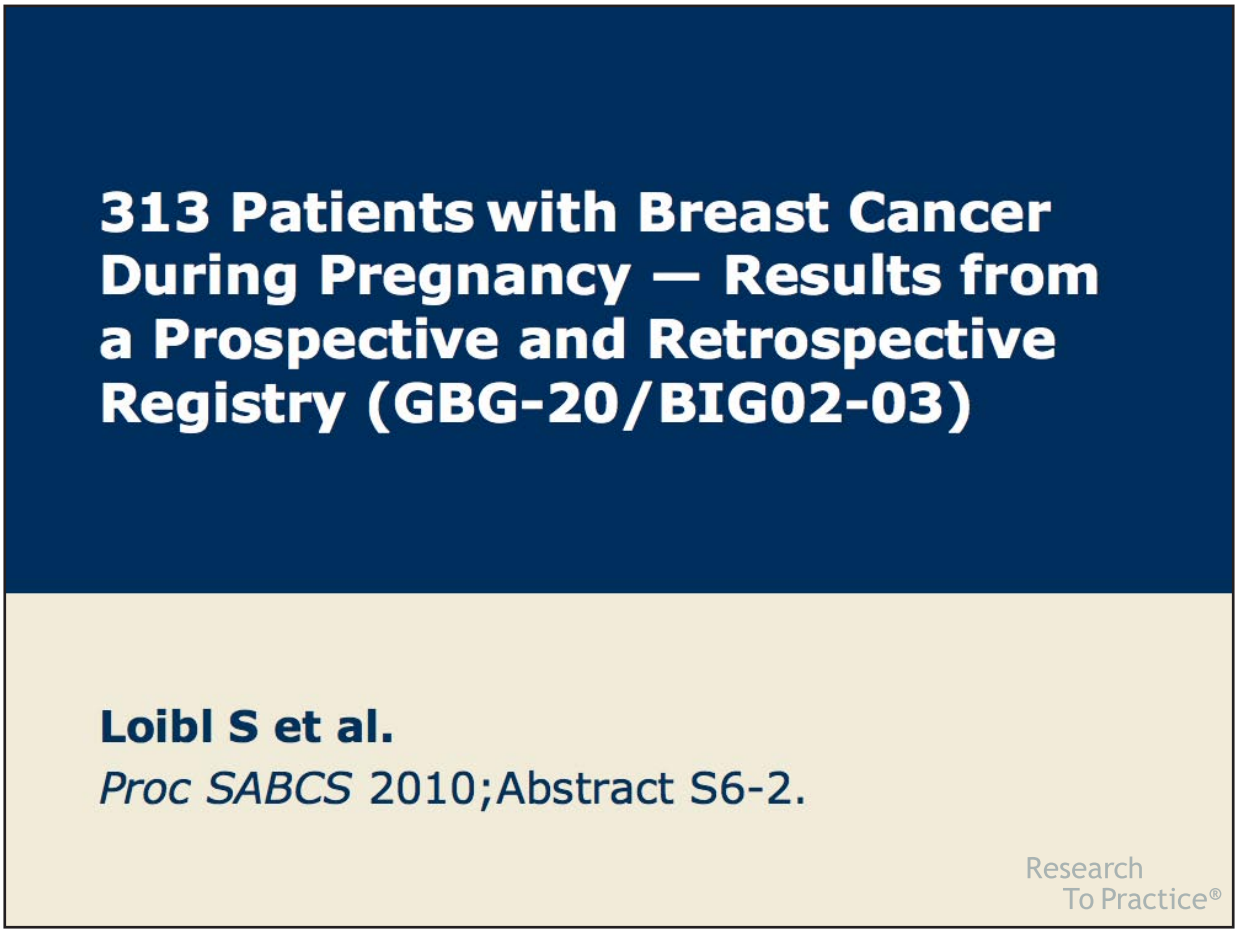
A Prospective and Retrospective Registry of Pregnant Patients with Breast Cancer

Presentation discussed in this issue

Loibl S et al. **Patients with breast cancer during pregnancy — Results from a prospective and retrospective registry (GBG-20/BIG02-03).** San Antonio Breast Cancer Symposium 2010;**Abstract S6-2**.

Slides from a presentation at SABCS 2010 and transcribed comments from a recent interview with Harold J Burstein, MD, PhD (12/22/10)



Methods

- **Study design**
  - A registry of retrospectively and prospectively collected data
- **Objective**
  - To increase the evidence for treatment of breast cancer during pregnancy
- **Eligibility**
  - All patients diagnosed with breast cancer during pregnancy independent of treatment and gestational age

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

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Endpoints

- **Primary**
  - Fetal outcome 4 weeks after delivery
- **Secondary**
  - Maternal outcome of pregnancy
  - Stage at presentation and biological characteristics
  - Breast cancer therapy and type of surgery
  - Mode of delivery (vaginal vs caesarean)
  - Outcome of the newborn 5 years after delivery
  - Breast cancer outcome 5 years after diagnosis

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

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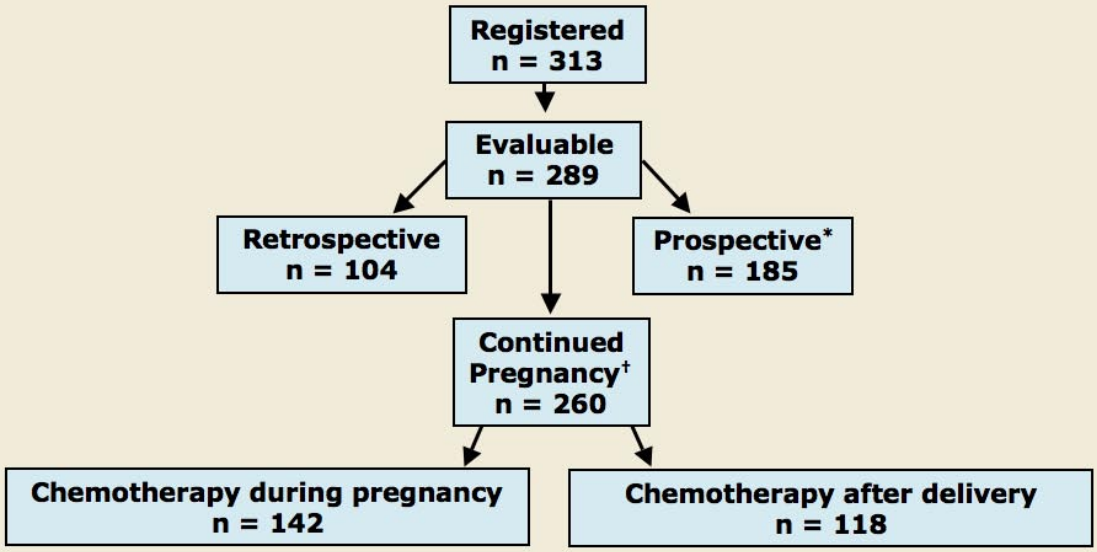
Flow Diagram of Patients



* Patients diagnosed after April 2003 were defined as prospective
† Abortion or miscarriage (n = 29)

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

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Baseline Characteristics

	All patients n = 260	Chemotherapy during pregnancy n = 142	Chemotherapy after delivery n = 118
Age, median	34 years	34 years	33 years
T-status 1 or 2	69.9%	62.8%	76.2%
Node-positive	48.1%	51.4%	40.0%
Ductal subtype	97.1%	98.6%	95.8%
Grade III	64.4%	63.9%	66.7%
ER-negative	60.9%	59.9%	63.9%
HER2-positive	42.2%	43.0%	42.2%

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

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Obstetrical Characteristics

	All patients n = 289	Prospective n = 185	Retrospective n = 104
Time of diagnosis, gestation week	23 weeks	24 weeks	20 weeks
Abortion or miscarriage	10.0%	10.8%	8.7%
Caesarean delivery	48.7%	44.4%	56.1%
Mastectomy	50.4%	49.1%	52.7%

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

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Chemotherapy During Pregnancy (n = 142)

Regimen	AC/EC	FE(A)C	CMF	Vinca alkaloids	E/A monotherapy	Taxanes
Patients, n	71	29	14	12	10	6

Cycles	1	2	3	4	5	6	8
Patients, n	8	25	23	52	14	19	1

- A total of 527 cycles were given.
- The median number of cycles was 4.

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

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Delivery Outcome

	All patients n = 260	Chemotherapy during pregnancy n = 142	Chemotherapy after delivery n = 118
Time of diagnosis, gestation week	—	20 weeks	28 weeks
Median week of delivery, (range)	36 (30-42)	37 (31-42)	36 (30-42)
Median birth weight	2,772 grams	2,810 grams	2,730 grams
Premature deliveries*	24.0%	16.9%†	33.0%†

* Before 35th week
† $p = 0.009$ for chemotherapy during pregnancy vs after delivery

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

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Selected Newborn Events

Events	Chemotherapy during pregnancy (n = 142)	Chemotherapy after delivery (n = 118)	*p*-value
Total*	17 (12%)	8 (6.7%)	0.16
Congenital malformations†	3	1	—
Trisomy-18	1	0	—
Persistent foramen ovale	2	0	—
Infections	4	0	—
Neutropenia	2	1	—
Anemia	2	0	—
Necrotic enterocolitis	1	0	—

*Eight and five newborns that were prematurely delivered experienced an event in the chemotherapy during versus chemotherapy after delivery groups, respectively; †Polydactylia (n = 2), rectal atresia (n = 1), hypospadia (n = 1)

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Author Summary

- More than 50% of the patients received chemotherapy during pregnancy (median = 4 cycles)
- 77% received an anthracycline-based regimen
  - Only six patients received a taxane during pregnancy
- Premature deliveries were significantly greater in the no chemotherapy group compared to the chemotherapy group (p = 0.009), most likely to allow patients to begin treatment following delivery.
- Fetal outcomes were comparable between the groups treated during or after pregnancy.
  - Total newborn events, 17 vs 8 (p = 0.16)
- Survival outcomes are comparable between patients treated during or after pregnancy (data not shown).

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

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Author Conclusions

- Premature delivery increasing fetal morbidity and unfavorable long-term outcome is unnecessary.
- Pregnant patients should receive treatment that follows as closely as possible the standard recommendations for non-pregnant women.

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

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Investigator Commentary: Breast Cancer During Pregnancy

There is probably no clinical circumstance in breast cancer medicine that's more frightening for the patient and for the doctor than breast cancer during pregnancy, because it can be tougher to diagnose the tumor due to the physiologic changes in the breast that accompany pregnancy and because of the risks that the cancer treatments and diagnostic evaluations might have on the baby. So little is known about breast cancer during pregnancy that almost any meaningful data are welcome.

The German Breast Group collected data from their registry experience to track outcomes of women who were diagnosed with breast cancer during pregnancy. They demonstrated that it is feasible to administer several chemotherapy regimens to patients who absolutely need it during their pregnancy, particularly in the second and third trimesters. The investigators also attempted to characterize how the infants fared who were born having been exposed to chemotherapy. For the most part, no major findings arose of congenital anomalies or major adverse events seen in those infants. Some infants had a variety of short-term medical issues, but we must be concerned that the small sample size makes it difficult to exclude the possibility that chemotherapy didn't have subtle adverse effects on these babies.

Interview with Harold J Burstein, MD, PhD, December 22, 2010