5 Minute JournalClub

Key SABCS Presentations

Issue 8, 2011

Discordance in Hormone Receptor and HER2 Status in Breast Cancer During Tumor Progression

For more visit ResearchToPractice.com/5MJCSABCS2011

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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 OBJECTIVES

- Recognize the rate of discordance in ER and HER2 status between primary breast cancer and sites of tumor relapse.
- Counsel patients with recurrent breast cancer about the clinical implications of biomarker discordance and the role of repeat biopsy, when feasible.

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No real or apparent conflicts of interest to disclose.

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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 metastatic breast cancer

The use of tissue assays to identify patients most likely to respond to specific therapies has markedly increased following a series of reports on genomic alterations in EGFR and EML4-ALK in lung cancer, K-ras in colorectal cancer, B-raf in melanoma and a host of factors in hematologic cancers, including and most recently CD30 in Hodgkin lymphoma and anaplastic large cell lymphoma.

Of course, the grandmother of "personalized oncology" is breast cancer, and while ER and HER2 testing are classic models of tissue predictors, we have seen reams of data over the years to shake our confidence in almost every ER/HER2 result obtained. **An intriguing new data set from Sweden** raises even more concern, demonstrating again that it is not uncommon for ER and to a lesser extent HER2 to be different in a biopsied metastasis than in the previous primary tumor. In this study discordance was observed in approximately one third of patients. However, what this means exactly in terms of treatment decision-making is uncertain and under active debate.

It seems plausible that patients with a prior negative assay might respond to targeted treatment if the marker is detected in the met, but it's not clear if the reverse (which is more common) is true. With few data to go on, many clinicians follow the "Cliff Hudis Rule" — if a patient with breast cancer has ever had a positive ER or HER2 result, she likely should receive at least one course of the appropriate targeted treatment in the relapsed disease setting, regardless of the most recent assay result.

Another critical issue related to rebiopsy is ruling out another cause of what seems to be recurrence. Many groups, including the Swedes, have shown that things are not always as they appear, and my favorite example of this phenomenon relates to a case presented at one of our CME symposia several years ago by Bill Reeves, an oncologist from Youngstown, Ohio. The patient had received chemotherapy for node-positive breast cancer three years earlier and presented with early satiety and several space-occupying lesions in the liver. Rather than assume the obvious, Bill had a needle placed and discovered that the hepatic disease was in fact GIST (with an occult gastric primary tumor later detected). Dr Reeves quickly altered his clinical thinking, and the patient went on to have an excellent response to imatinib.

Clearly the decision to rebiopsy any patient with apparent metastatic disease is multifactorial with a critical issue being the ease or difficulty of accessing tissue, but our Patterns of Care surveys have demonstrated frequent use of rebiopsy in clinical practice both for accurate diagnosis and repeat tissue biomarker assays. In addition to this thought-provoking Swedish study, the following interesting papers on metastatic breast cancer were presented in San Antonio:

1. **Denosumab (D-mab)**

A randomized, Phase III placebo-controlled trial demonstrated an 18 percent relative risk reduction in skeletal events with this RANK ligand inhibitor compared to zoledronic acid (ZA) with the risk of pathologic fracture decreasing from 28.1 percent to 23.5 percent and the risk of radiation to the bone dropping from 17.2 percent to 13.5 percent. Rates of osteonecrosis of the jaw (ONJ) were similar with D-mab (26 patients — 2.5%) and ZA (18 patients — 1.8%), but Grade 3/4 hypocalcemia was seen in 18 patients on D-mab (1.8%) versus 12 (1.2%) on ZA. In another bone-related study that followed a series of case reports, the group from Roswell Park presented their experience with ONJ in patients on bisphosphonates versus those on bisphosphonates/ bevacizumab, and the severity and dental outcome appeared quite similar in the two groups, which is reassuring given the issue of wound healing with bev.

2. **Endocrine treatment combined with targeted therapy**

For years, investigators have been proposing the combined use of biologic and hormonal agents to subvert endocrine resistance, but two recent randomized studies provided lukewarm or no support for the concept. One small trial seemed to show a modest benefit when the mTOR inhibitor everolimus was combined with tamoxifen, while another study of fulvestrant plus lapatinib was flat-out negative, although there was a suggestion of benefit in patients with HER2-positive tumors.

3. **More on bevacizumab**

A meta-analysis focusing on cardiovascular events in randomized studies of chemotherapy with or without bevacizumab in the metastatic disease setting demonstrated the expected risk of hypertension but also a modest but statistically significant increase in left ventricular dysfunction. Rates of arteriothrombotic events were not statistically different. Another Phase II study demonstrated good tolerability and encouraging efficacy when docetaxel 75 mg/m^2 was combined with bevacizumab in HER2-negative disease, as well as when trastuzumab was added to the regimen in patients with HER2-positive tumors.

This concludes our brief series on the happenings in San Antonio. Stay tuned for another experiment in CME as we are set to launch a new four-part series on GI cancers using what we think is an innovative, interesting and different web-based platform.

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Discordance in Hormone Receptor and HER2 Status in Breast Cancer During Tumor Progression

Presentation discussed in this issue

Lindstrom LS et al. **Discordance in hormone receptor and HER2 status in breast cancer during tumor progression.** San Antonio Breast Cancer Symposium 2010;**Abstract S3-5**.

Slides from a presentation at SABCS 2010 and transcribed comments from Lisa A Carey, MD (12/12/10)

Background and Methods

- Management of metastatic breast cancer (mBC) is routinely based on primary tumor ER/PR and HER2 status.
  - Alterations in these predictive factors for therapy may lead to altered management.
- **Methods:**
  - Patients (n = 1,051) with breast cancer experiencing relapse from 1997-2007 and reported to the Stockholm-Gotland Breast Cancer Registry were investigated.
  - Biochemical, IHC or immunocytochemical (ICC) methods were used for determination of ER and PR.
  - Primary tumor HER2 status investigated using IHC with two or three monoclonal antibodies, confirmed by FISH for IHC 2+ and 3+ and recurrences using ICC or FISH.
- **Aim:**
  - To determine if hormone receptors and HER2 expression profiles change between primary breast tumor (Prim) and relapse (Rel).

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

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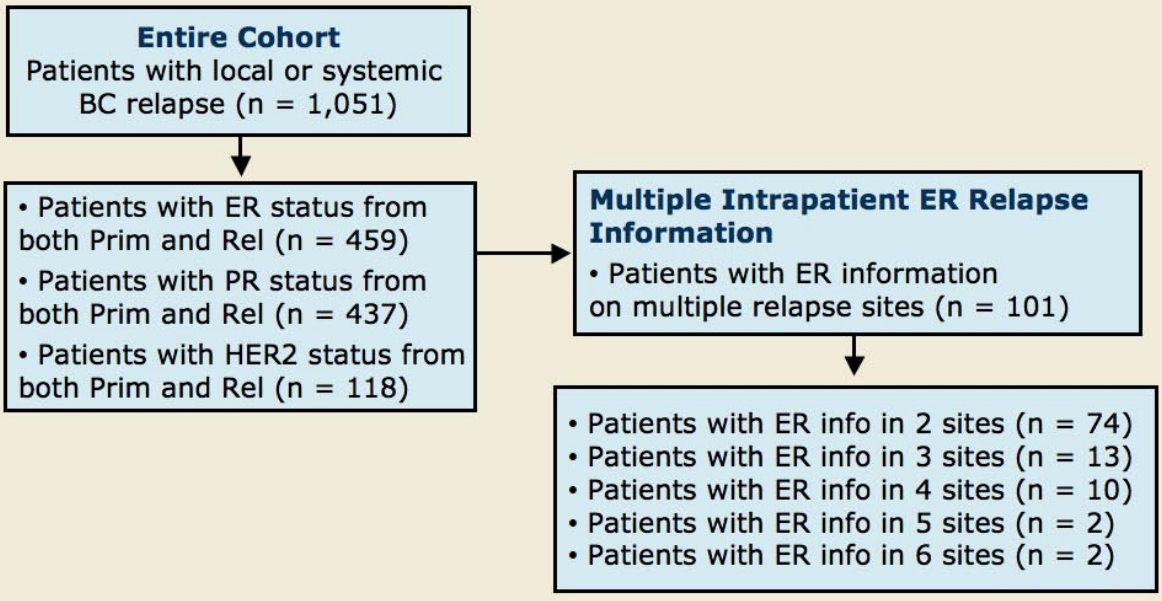
Hormone Receptor and HER2 Cohort



Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

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Intraindividual ER and HER2 Status in Primary Tumor and Relapse

ER status	Local and systemic relapse n = 459	Systemic relapse only n = 335
Prim(+)/Rel(+)	44.0%	39.1%
Prim(+)/Rel(-)	26.4%	30.7%
Prim(-)/Rel(+)	6.7%	6.3%
Prim(-)/Rel(-)	22.9%	23.9%
HER2 status	**n = 118**	**n = 98**
Prim(+)/Rel(+)	21.2%	18.4%
Prim(+)/Rel(-)	6.8%	6.1%
Prim(-)/Rel(+)	3.4%	4.1%
Prim(-)/Rel(-)	68.6%	71.4%

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

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ER Status Change between First and Subsequent Relapses*

ER status change	n	%
Stable positive	34	33.7%
Stable negative	38	37.6%
Positive to negative	11	10.9%
Negative to positive	12	11.9%
Heterogeneity†	6	5.9%
Total	101	100%

* ER status between different relapse sites in the same patient were assessed, using the ER status of the first relapse site as the basis of comparison.

† Includes patients who had discordant ER status between subsequent relapse sites.

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

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Risk of Death Depending on Intraindividual ER Status in Primary Tumor and Systemic Relapse

Intraindividual primary tumor and metastasis	Patients (n)	Deaths overall	OS from BC diagnosis to death or censoring	OS from mBC diagnosis to death or censoring
ER status			HR (95% CI)	HR (95% CI)
Prim(+)/Met(+)	131	54	Reference	Reference
Prim(+)/Met(-)	103	61	1.40 (1.00-1.98)	1.33 (0.90-1.98)
Prim(-)/Met(+)	21	9	0.87 (0.44-1.72)	1.06 (0.49-2.28)
Prim(-)/Met(-)	80	44	1.27 (0.79-2.05)	1.21 (0.69-2.12)

* Adjusted for age and calendar year of diagnosis, PR, tumor classification, tumor stage, lymph node metastasis, hormonal therapy and chemotherapy

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

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Author Conclusions

- Every third patient experienced a change in hormonal receptor status, and one patient in 10 experienced a change in HER2 status during tumor progression.
- Intraindividual primary and relapse ER and PR status were significantly associated with differential survival (data not shown).
- Patients losing ER positivity had an increased risk of dying compared to patients with stable ER-positive disease.
- Our data combined with the data from other groups demonstrate that morphological verification of biomarker profiles of suspected metastatic breast cancer lesions will improve diagnostic precision and personalized management.

Lindstrom LS et al. *Proc SABCS* 2010;Abstract S3-5.

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Investigator Commentary: Discordance in Hormone Receptor and HER2 Status between the Primary Breast Cancer Tumor and Metastases

One of the themes that emerged in 2010 was the question: Does the cancer change over time? And of course we want to focus on changes that are clinically meaningful.

Data presented at ASCO 2010 in addition to a presentation by Lindstrom and colleagues at San Antonio evaluated changes in clinically relevant markers between the primary tumor and metastatic disease. If you evaluate these data — again, Dr Lindstrom's data set focused on ER and HER2 — you find small but real and consistent changes in relevant markers between the primary breast tumor and metastatic disease. I believe rebiopsying at the time of relapse is a reasonable approach. The main reason to rebiopsy is to ensure you're treating what you think you're treating, as a number of conditions can masquerade as metastatic breast cancer.

I also believe rephenotyping to be of value, but you have to be cautious in using it to guide therapy. For example, a hormone receptor-positive breast tumor that's negative on rebiopsy may or may not reflect endocrine-insensitive disease.

Presentation by Lisa A Carey, MD, SABCS December 12, 2010

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