5 Minute JournalClub

Key SABCS Presentations
Issue 6, 2011

Capecitabine (Seven On, Seven Off) with Lapatinib for Metastatic Breast Cancer Refractory to Trastuzumab

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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

- Cite the rates of response and toxicity seen with the combination of lapatinib and a novel schedule of capecitabine in patients with HER2-positive metastatic breast cancer refractory to trastuzumab.

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Click here for SABCS papers on HER2-positive breast cancer

View from Breast Cancer Think Tank toward Biscayne Bay and South Beach 7:30 AM February 4, 2011 (photo by Hope Rugo)

In 2003, my CME compatriots and I moved out of our University of Miami offices with the goal of creating a unique environment that would inspire us and others to think differently about cancer treatment, research and education. We found a too-good-to-be-true sublease from a troubled bank in one of the oldest office buildings in South Florida with creepy "Tower of Terror" elevators but an unforgettable view. One of the ways we envisioned putting these cozy confines to good use would be to bring together clinical investigators, encourage a casual dress code and invite everyone to share what's most on their mind. At our recent breast cancer Think Tank, that is exactly what

happened as Melody Cobleigh presented two very informative and interesting cases that have been occupying a significant amount of space in her head.

The first was a 25-year-old graduate student seeking another opinion for ER-negative, HER2-positive locally advanced breast cancer. At the Think Tank, the faculty agreed that chemo/trastuzumab was indicated and Dr Cobleigh relayed the good news that after one cycle of TCH most of the disease had receded. She then threw a wrench into the works by revealing that the repeat HER2 assay done at her institution was reported as negative (IHC 2+, FISH not amplified with a ratio of 1.2). Most of the faculty, including Dr Cobleigh, were nervous about discontinuing trastuzumab for obvious reasons, but there was also some sentiment in the other direction.

The other patient was a 58-year-old woman who had received adjuvant chemo and tamoxifen for an ER-positive, HER2-negative tumor that came roaring back in the form of extensive liver and bone mets. Dr Cobleigh ordered a liver biopsy that confirmed recurrence, but this time the tissue was read again as ER-positive but also HER2-positive. The patient went on to have a series of responses to anti-HER2 treatment alone or with chemo, but eventually she ran out of options and was rapidly deteriorating when a new trial became available using the immune conjugate T-DM1. Amazingly, this woman had a major tumor response and significant relief of symptoms, and much to everyone's surprise, at the time of the Think Tank she was hiking in Arizona on vacation. One can only imagine what the outcome might have been had Dr Cobleigh not obtained the liver biopsy and documented HER2-positive disease.

These patients are good examples of the increasing complexity, uncertainty and challenge associated with the management of HER2-positive breast cancer. In this issue of our series, we summarize a number of related reports from San Antonio that provide optimism, but also as many questions as answers about HER2-positive disease.

1. **Two important papers on HER2 testing**

These complicated and detailed studies analyzing tissue from patients enrolled in the ongoing ALTTO trial and previously reported adjuvant NCCTG and BCIRG trials demonstrate that Dr Cobleigh's patients are not rare, as some discordance in HER2 test results was seen even between central reference labs.

2. **Adjuvant trastuzumab in older patients; long-term management of metastatic disease**

A German report from a prospective observational study demonstrated comparable outcomes for "elderly" — defined as 65 and over — and younger patients receiving adjuvant trastuzumab. One might question the definition of elderly in this trial and wonder if data should be reported as in myeloma — above and below age 75 (the new 65). In any event, this study confirms what investigators have been saying for years — if fit older patients are managed carefully, they tolerate treatment well and derive similar benefit. The other papers provide more support that in metastatic disease, continuing anti-HER2 treatment indefinitely beyond progression adds benefit and is widely used in practice.

3. **More on T-DM1 and pertuzumab**

Based on a Dana-Farber study of 23 patients, Dr Cobleigh can anticipate that if and when her patient on T-DM1 develops progressive disease, further response to additional anti-HER2 treatment is likely. A future noncytotoxic option for HER2-positive disease might be the dual targeted approach reported in a Phase II study at San Antonio demonstrating that in 67 patients T-DM1 and pertuzumab can be combined and tolerated in full doses. Perhaps more importantly, the trial revealed a 57 percent objective response rate with this interesting combination in the first-line setting.

4. **Novel schedule of lapatinib/capecitabine**

Investigators at Memorial Sloan-Kettering have long been interested in the capecitabine schedule of seven days on, seven days off (7-7), and this Phase II study achieved encouraging results when capecitabine 7-7 was combined with daily lapatinib. A planned Phase III trial will compare the 7-7 schedule to the classic 14 days on, seven days off regimen.

Next up on *5-Minute Journal Club*: Several increasingly rare reports on adjuvant chemotherapy, including the role (or lack thereof) of adding in capecitabine.

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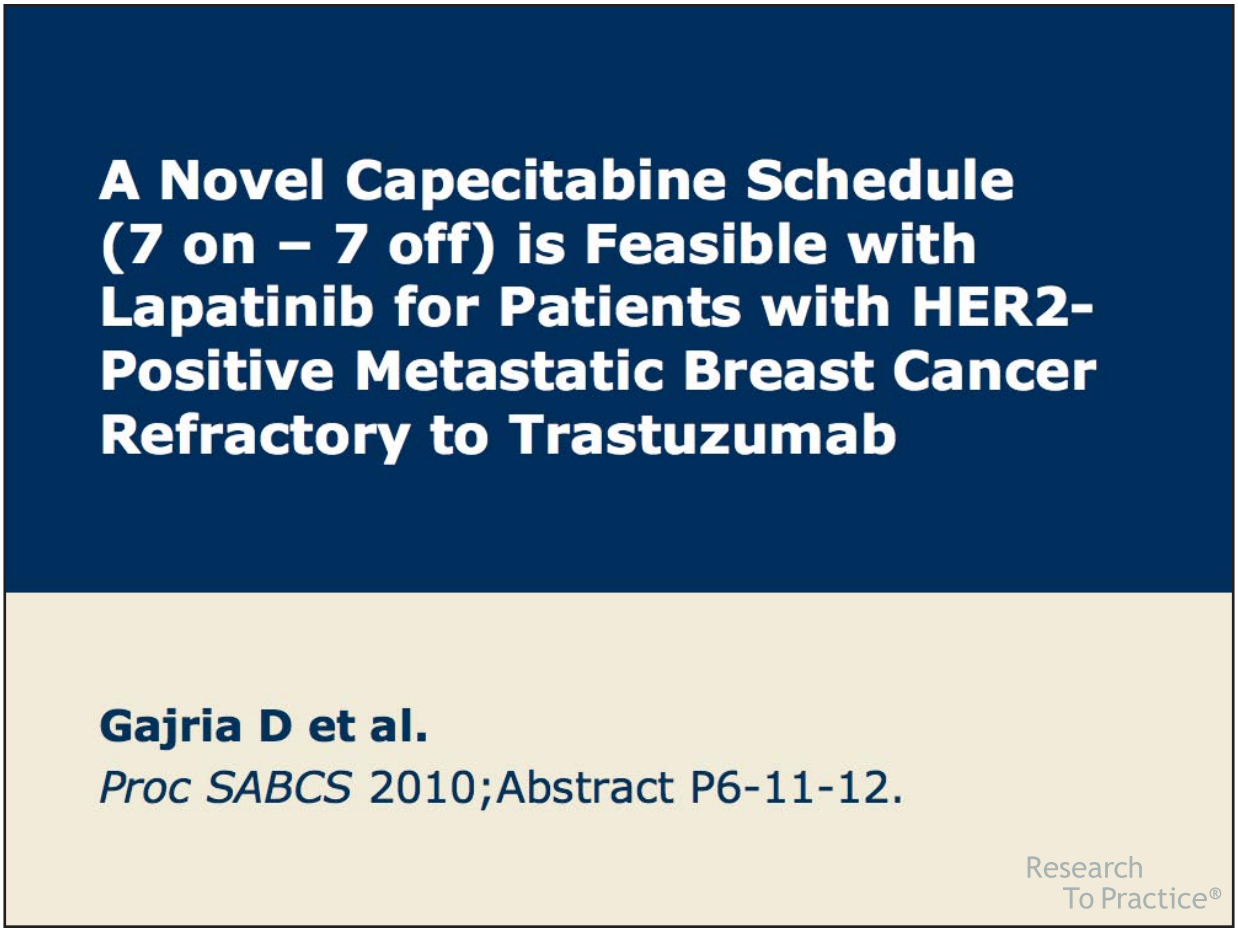
Capecitabine (Seven On, Seven Off) with Lapatinib for Metastatic Breast Cancer Refractory to Trastuzumab

Presentation discussed in this issue

Gajria D et al. **A novel capecitabine schedule (7 on — 7 off) is feasible with lapatinib for patients with HER2-positive metastatic breast cancer refractory to trastuzumab.** San Antonio Breast Cancer Symposium 2010;**Abstract P6-11-12**.

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



Objectives

- **Hypothesis**
  - Lapatinib in combination with an optimal schedule of capecitabine 7 days on, 7 days off (7-7) will be feasible and active in patients with HER2-positive metastatic breast cancer refractory to trastuzumab.
- **Primary endpoint**
  - To evaluate complete and partial response rates according to RECIST criteria.
- **Secondary endpoints**
  - Toxicity
  - Stable disease for more than 6 months
  - Progression-free survival at 6 months

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

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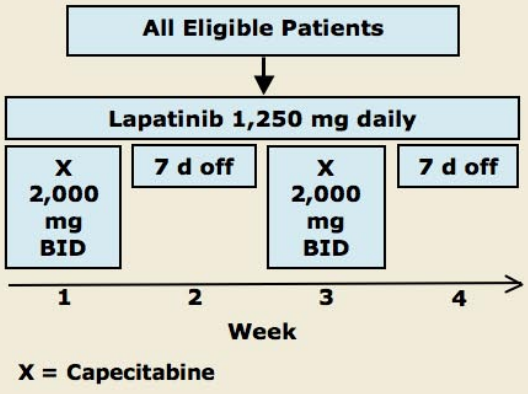
Study Design

Accrual: 23 (Closed)*

Eligibility
Metastatic breast cancer (mBC)
HER2-positive (IHC3+ or FISH>2)
Disease progression following trastuzumab
No more than 2 prior chemotherapy regimens
No prior use of fluoropyrimidine for metastatic disease
LVEF ≥50% by MUGA scan



* Study closed to further accrual due to slower than expected accrual and an anticipated randomized Phase III trial comparing capecitabine (7–7) to standard capecitabine dose (14 days on, 7 days off)

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

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Patient Characteristics

	n = 23
Median age, years (range)	54 (34-72)
Median ECOG PS (range)	0 (0-2)
ER- or PR-positive, n	13
HER2-positive, n	23
Sites of metastases, n Visceral metastases Brain metastases	 16 3
Median number of prior regimens for mBC (range)	1 (0-2)

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

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Best Response

Outcome	Patients n = 23
Complete response	0
Confirmed partial response	4 (17%)
Stable disease, >6 months	6 (26%)
Stable disease, <6 months	12 (52%)
Progressive disease	1 (4%)

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

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Treatment Modifications

Outcome	Patients n = 23
Discontinued treatment due to toxicity*	4
Capecitabine dose reductions or delays	10
Lapatinib dose reductions or delays	3
LVEF declines requiring treatment modification	0

*Grade 2 LFTs, Grade 2 hand-foot-mouth syndrome and Grade 2 rash associated with lapatinib

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

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Adverse Events

Toxicity	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	2 (9%)	1 (4%)	1 (4%)
Hand-foot syndrome	9 (39%)	1 (4%)	0
Thrombocytopenia	0	1 (4%)	0
Neutropenia	0	1 (4%)	0
Diarrhea	6 (26%)	0	0
Liver dysfunction	4 (17%)	0	0
Fatigue	2 (9%)	0	0
Nausea	1 (4%)	0	0
Vomiting	0	0	0

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

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Author Conclusions

- Capecitabine 7-7 plus lapatinib demonstrates activity and feasibility in patients with HER2-positive, trastuzumab-refractory, metastatic breast cancer.
  - Confirmed partial response rate = 17%
  - Stable disease >6 months = 26%
- The combination of capecitabine 7-7 and lapatinib was associated with mild gastrointestinal toxicity.
  - No reports of ≥Grade 3 nausea, vomiting or diarrhea
- These data have informed the design of a Phase III study that will evaluate capecitabine 7-7 versus standard capecitabine dosing (14 days on/7 days off).

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

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Investigator Commentary: Capecitabine (7 on, 7 off) with Lapatinib in HER2-Positive mBC Refractory to Trastuzumab

This study from Memorial Sloan-Kettering was based on mathematical modeling, which suggested that capecitabine administered on a seven days on, seven days off schedule may be more efficacious and tolerable than the standard 14 days on, seven days off schedule. The investigators evaluated an all-oral regimen with the 7/7 schedule of capecitabine in combination with lapatinib in patients with HER2-positive metastatic breast cancer that was refractory to trastuzumab.

They demonstrated that the combination was feasible, with response rates of approximately 20 percent. Their experience is not large enough to make any definitive conclusions, although much larger studies have evaluated this combination but not with this schedule of capecitabine. The side effects observed in this study were mild, with some hand-foot syndrome but no significant diarrhea or nausea/vomiting. It's a small study, but it suggests that lapatinib can be combined with this novel schedule of capecitabine.

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