5 Minute JournalClub

Efficacy of Administering Preoperative Hydroxyprogesterone in Women with Operable 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

- Summarize the effect on survival of administering a preoperative hydroxyprogesterone injection in women with operable 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:

George W Sledge Jr, MD
Ballve-Lantero Professor of Medicine
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Advisory Committee: Bristol-Myers Squibb Company, Genentech BioOncology.

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This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Genentech BioOncology, Genomic Health Inc and GlaxoSmithKline.

Last review date: February 2010
Expiration date: February 2011

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5 MinuteJournalClub

IN THIS ISSUE:

• **New analysis** from MA17 trial demonstrates significant benefit of an AI after five years of tamoxifen in women premenopausal at diagnosis

• **Neoadjuvant progesterone** reduces breast cancer relapse rate by mimicking the luteal phase of the menstrual cycle

• **Tamoxifen** as chemoprevention: This time it makes sense...in lung cancer

In 1990, I traveled to Bethesda for an NCI Consensus Conference on breast cancer, and managed to arrange a joint interview with the King and Queen of tamoxifen, Mike Baum and Helen Stewart. Both of these noted investigators were in town presenting findings from Phase III randomized trials they led demonstrating what the chemo-oriented oncology world of that era had a very hard time swallowing — namely that a fairly nontoxic treatment then employed for palliation of metastatic disease could, if used as adjuvant therapy, have an impressive impact on breast cancer recurrence and death.

Working on the other side of the pond, Mike managed to pull off two trials in the UK while Helen ran the landmark Scottish study, and their data demonstrated the benefit of tamoxifen in both pre- and postmenopausal patients. However, there was another key European hormonal player whose work was considered the gold standard for evidence — the soon-to-be-knighted Sir Richard Peto, who was able to convince (without email or the web) virtually every investigator who had previously done a randomized trial in early breast cancer to provide individual patient data that the Oxford minions then "cleaned up" and wove into forest plots that ultimately defined treatment standards in that era of smaller trials.

This laborious work became in 1985 the first breast cancer Worldwide Overview, in which Peto clearly demonstrated that postmenopausal patients treated with tamoxifen experienced a major survival benefit. However, even by 1990 the Overview did not demonstrate an OS advantage in premenopausal women, and for this reason many investigators cautioned against prescribing Tam to younger women. However, Mike, Helen and Sir Richard all knew that the most likely explanation for the lack of a survival benefit was not that the agent didn't work in that setting, but more likely that not

enough events had yet been observed, simply because there are fewer pre- than postmenopausal patients.

During that 1990 interview conducted at an ancient Holiday Inn across from the NIH, Helen, and particularly Mike, were totally apoplectic about the premenopausal issue and almost jumped across the table imploring listeners to treat these patients with a relatively safe and well-tolerated agent that had the potential to cut the relapse rate in half.

However, Patterns of Care studies at that time (yes, we did those then) demonstrated that younger women pretty much weren't receiving adjuvant tamoxifen until 1995, when more events were eventually accrued to the Overview, and Mike and Helen's assertions played out exactly as predicted. In an instant, Tam became standard for premenopausal patients with ER-positive tumors. I remember doing some pretty scary mental math back then adding up the number of young women who likely died during the 10 years spanning the 1985 and 1995 Overviews, when premenopausal patients finally received the blessings of the evidence-based pontiffs.

These nightmares returned a few months ago in San Antonio, when Paul Goss presented a **new analysis** from the historic MA17 study of letrozole after five years of adjuvant tamoxifen. To enter the trial, patients had to be postmenopausal at the randomization point but could have been premenopausal at the time of diagnosis, and in that subset, the effect of a delayed AI was equal to and perhaps even greater than it was in primary postmenopausal patients.

In the seven years since first presenting MA17, Paul has continually professed his belief that ER-positive breast cancer is a lifelong remitting and relapsing disease not unlike follicular lymphoma, and that the potential impact of prolonged endocrine treatment may be far greater than most realize. His pioneering work has demonstrated that hormonal interventions many years after diagnosis can profoundly impact clinical outcome, and he has cautioned us not to look at the breast cancer "golf ball" 10 yards off the tee but when "it lands on the fairway 20 years later."

Paul points out that the biologic model of ER-positive disease is unlikely to be different in pre- and postmenopausal patients, but our Patterns of Care studies demonstrate that premenopausal patients rarely receive more than five years of hormone therapy, and there is a lack of clinical research and a lot of confusion about management of patients who cease menses during tamoxifen — in some cases after chemo — and of the uncommon but important scenario of a woman who is still premenopausal after five years of tamoxifen.

And so it goes. More fodder for debates, roundtables and publications, but in the back of my head an old tune plays, and it brings back bad memories.

Next up on 5-Minute Journal Club...well, this marks the conclusion of our short and hopefully sweet review of the best from San Antonio. Please take a moment and tell us candidly what you liked and didn't like about this craziness and check out our new **web-video-slide program** in six tumor types, "Year in Review," profiling the most important papers and publications of the past year.

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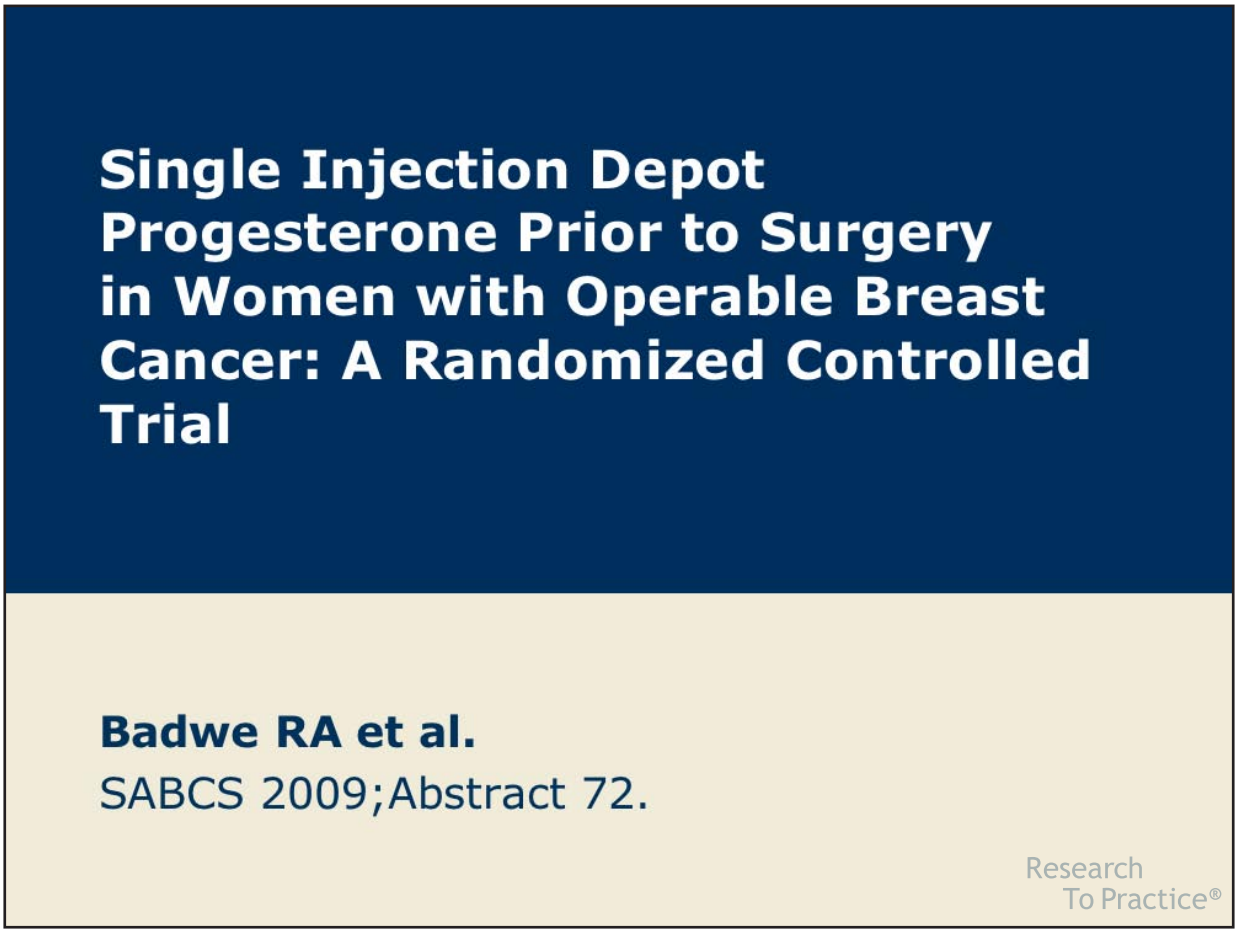
Efficacy of Administering Preoperative Hydroxyprogesterone in Women with Operable Breast Cancer

Presentation discussed in this issue

Badwe RA et al. **Single injection depot progesterone prior to surgery in women with operable breast cancer: A randomized controlled trial.** San Antonio Breast Cancer Symposium 2009;**Abstract 72**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with George W Sledge Jr, MD (2/15/10)



Introduction

- Meta-analysis of 37 retrospective studies demonstrated a 15% reduction in mortality (p=0.0003) for patients undergoing surgery during progestogenic phase (*Surg Clin North Am* 1999;79:1047).
- Meta-analysis of the effect of circulating progesterone at the time of surgery showed a 54% survival benefit (p=0.002) when progesterone levels were high in women that were node-positive (*Surg Clin North Am* 1999;79:1047).
- Two recent prospective studies did not find an association between timing of breast cancer surgery during the menstrual cycle and survival (*JCO* 2009;27:3620, *BJC* 2008;98:39).
- **Current study objective**
  - To evaluate the effect of pharmacologically inducing a progestogenic environment at the time of surgery on survival in women with operable breast cancer (OBC).

Badwe RA et al. SABCS 2009;Abstract 72.

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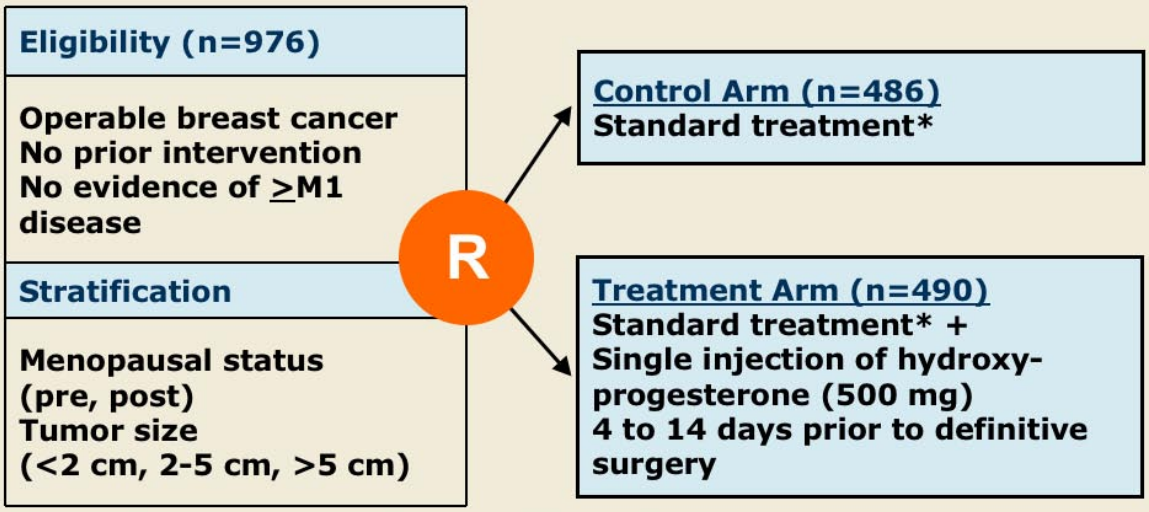
Randomized Trial of Preoperative Hydroxy-progesterone



**Standard international guidelines were followed for adjuvant treatment.*

Badwe RA et al. SABCS 2009;Abstract 72.

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Recurrences and Deaths (median follow-up 65 mos)

Recurrences	Treatment	Control
All Patients (n=490, 486)	128 (26.1%)	145 (29.8%)
Lymph-node positive (n=239, 232)	83 (34.7%)	105 (45.2%)
Deaths		
All Patients (n=490, 486)	97 (19.8%)	105 (21.6%)
Lymph-node positive (n=239, 232)	58 (24.3%)	77 (33.1%)

Badwe RA et al. SABCS 2009;Abstract 72.

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Efficacy Results (median follow-up 65 mos)

All patients	Treatment (n=490)	Control (n=486)	Hazard Ratio	95% CI	*p*-value
Disease-free survival	73.9%	70.2%	0.87	0.68-1.09	0.23
Overall survival	78.4%	80.2%	0.92	0.69-1.21	0.53
Patients with lymph node-positive disease	**Treatment (n=239)**	**Control (n=232)**	**Hazard Ratio**	**95% CI**	***p*-value**
Disease-free survival	65.3%	54.7%	0.72	0.54-0.97	0.02
Overall survival	75.7%	66.8%	0.70	0.49-0.99	0.04

Badwe RA et al. SABCS 2009;Abstract 72.

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Disease-Free Survival: Cox Proportional Hazard Model

Variable	Risk Ratio	*p*-value	95% CI
Primary tumor size	1.09	0.03	1.01-1.19
Nodal status	2.14	<0.0005	1.53-3.00
Treatment	0.60	0.29	0.24-1.52
Hormone receptor status	1.35	0.006	1.09-1.67
Treatment x nodes	1.16	0.03	1.10-1.33

Badwe RA et al. SABCS 2009;Abstract 72.

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Conclusions

- Induction of a progestogenic environment at the time of surgery significantly improved both disease-free and overall survival in women with lymph node-positive OBC.
  - Disease-free survival: 65.3% versus 54.7% (p=0.02)
  - Overall survival: 75.7% versus 66.8% (p=0.04)
- Disease-free survival is significantly impacted by:
  - Tumor size
  - Lymph node metastases
  - Hormone receptor positivity
  - Interaction between treatment and lymph node metastases
- This approach could be a simple, inexpensive and life-saving intervention for women with OBC.

Badwe RA et al. SABCS 2009;Abstract 72.

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DR SLEDGE: There have been a large number of papers over the years that have examined whether a relationship exists between the timing of the menstrual cycle when a patient has surgery and the ultimate outcome. Some studies have suggested that there is a relationship while other studies have not.

There are many methodologic issues with trying to determine where a patient is in her menstrual cycle. For many years, this was considered an interesting observation, but not one that could be investigated further. This study by Dr Badwe and colleagues is a fascinating new approach to addressing this observation.

It works on the assumption that if the timing of the menstrual cycle relationship is real, then artificially altering it around the time of surgery by administering a depot of progesterone may be beneficial to patients with breast cancer. Dr Badwe performed a controlled trial in which women about to enter surgery were randomly assigned to either receive depot progesterone or not.

To my surprise, this was a positive trial for the women who were administered progesterone. Indeed, in the subpopulation of women who had lymph node-positive disease, administration of progesterone resulted in a fairly dramatic improvement in long-term overall survival of about 10 percent.

I believe this is an interesting result that certainly deserves confirmation in other trials. If the result is correct, it doesn't necessarily mean that the initial hypothesis was correct, however. Large doses of progesterone could be affecting other receptors in addition to the estrogen receptor, and the results observed in this study may be mediated through some other receptor. I say this because the benefit in this trial appeared to be present both in patients with estrogen receptor-negative and in those with estrogen receptor-positive disease. For this to be a true result, it would have to be mediated via a different growth factor receptor within the steroid receptor superfamily.

DR LOVE: Are you aware whether any of the US cooperative groups plan to follow up on the results of this study?

DR SLEDGE: Not yet, but I'm sure that they will. This is too simple an intervention not to be followed up. This could be an intervention that would be readily accessible to every patient with breast cancer around the world. That is part of its fascination. In theory, it might well apply to both pre- and postmenopausal patients.

This study also brings up the issue of what happens during surgery. If the initial hypothesis is correct, it argues that the period around surgery is crucial in terms of metastogenesis. Many of us have issues with that as a hypothesis, because we know that in most cases women probably have microscopic metastatic disease for long periods before they ever see a physician. But it's possible that as a result of the

surgery itself, cytokines or growth factors are being released that affect microscopic metastatic sites. That's an interesting and testable hypothesis.

Dr Sledge is Professor of Medicine and Pathology at the Indiana University School of Medicine and Co-Director of the IUSCC Breast Cancer Research Program at Indiana University Simon Cancer Center in Indianapolis, Indiana.