7 Proffered Paper Oral

A randomized phase III trial of paclitaxel with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: Eastern Cooperative Oncology Group trial E2100

R. Zon[1], K. Miller[2], M. Wang[3], J. Gralow[4], M. Dickler[5], M. Cobleigh[6], E. Perez[7], T. Shenkier[8], N. Davidson[9]. [1]*Elkhart General Hospital, Elkhart, USA;* [2]*Indiana University Cancer Center, Indianapolis, USA;* [3]*Dana Faber Cancer Institute, Boston, USA;* [4]*Pudget Sound Oncology Consortium, Seattle, USA;* [5]*Memorial Sloan Kettering Cancer Center, New York, USA;* [6]*Rush University medical Centre, Chicago, USA;* [7]*Mayo Clinic, Jacksonville, USA;* [8]*British Columbia Cancer Agency, Vancouver Cancer Center, Vancouver, Canada;* [9]*Johns Hopkins Oncology Center, Baltimore, USA*

Purpose: Bevacizumab (Avastin®) is a humanized monoclonal antibody that inhibits vascular endothelial growth factor, the key mediator of tumor angiogenesis. Based on evidence of activity in late-stage metastatic breast cancer (MBC), a randomized phase III trial was designed to evaluate the efficacy and safety of combining bevacizumab with paclitaxel as first-line therapy in patients with locally advanced or metastatic breast cancer.

Methods: Patients were randomly assigned to receive paclitaxel 90 mg/m^2 on days 1, 8 and 15 of a 4-week cycle, either alone or in combination with bevacizumab 10 mg/kg on days 1 and 15. The primary endpoint was progression-free survival (PFS); response was assessed by RECIST criteria every 3 cycles. The study had 85% power to detect a 33% improvement in PFS assuming a one-sided type one error of 2.5%, requiring that 650 patients be recruited.

Results: From December 2001 to March 2004, 722 patients were enrolled; 680 patients were eligible. Baseline characteristics were well balanced between the treatment arms. This interim analysis, based on 484 events, shows that combining bevacizumab with paclitaxel significantly improves PFS (11.40 vs 6.11 months; HR = 0.51, $p < 0.0001$) and response rate (29.9% vs 13.8%, $p < 0.0001$) compared to paclitaxel alone. Immature survival data, based on 275 events, shows a trend toward improved overall survival with bevacizumab plus paclitaxel (28.4 vs 25.2 months; HR = 0.84, $p = 0.12$). Bevacizumab plus paclitaxel was generally well tolerated, although there was an increase in selected adverse events with combination therapy; grade 3/4 hypertension ≈16% vs 2% ($p < 0.0001$); grade 3/4 proteinuria 2.0% vs 0% ($p = 0.002$); and grade 3/4 bleeding ≈3% vs 0% ($p = 0.02$). The incidence of grade 3/4 thromboembolic events was low in both treatment groups (2% vs 4%). Bevacizumab plus paclitaxel did not compromise quality of life, assessed by FACT-B and FACT-G scores.

Conclusions: Bevacizumab plus paclitaxel significantly prolongs PFS compared to paclitaxel in untreated patients with MBC, with a minimal increase in toxicity.

Wednesday, 22 March 2006 14:15–16:00

SCIENTIFIC SESSION

Prevention strategies

8 Invited

Strategies to optimize tamoxifen use

A. Decensi[1,2], A. Argusti[1], B. Bonanni[2], A. Guerrieri-Gonzaga[2], M. Puntoni[1], S. Zanardi[1]. [1]*E.O. Ospedali Galliera, Division of Medical and Preventive Oncology, Genoa, Italy;* [2]*European Institute of Oncology – IEO, Chemoprevention Unit, Milan, Italy*

The activity of Tamoxifen (TMX) as a chemopreventive agent in women at high risk of breast cancer (BC) has been assessed in large phase III trials. TMX has been shown to reduce BC incidence by 30–40%, and is now approved for BC risk reduction. However, its use as a preventive drug has been limited due to safety concerns. Nonetheless, recent data on the long-term effects of TMX on cardiovascular mortality still provide the rationale for the use of this cheap and safe compound in breast cancer treatment.

Different strategies are being pursued to improve the efficacy of TMX in chemoprevention while decreasing toxicity. Simple means may be a dose reduction or an intermittent drug administration. Moreover, the combination of hormone replacement therapy (HRT) or of aromatase inhibitors (AIs) and TMX at low doses may represent another approach to overcome the risks while retaining the benefits of either agent.

The concept of a dose reduction has been assessed in a study of tamoxifen at standard dose (20 mg/day) and at two different lower doses (10 mg/day and 10 mg on alternate days) administered for two months to a cohort of 127 healthy women. No evidence of a dose response relationship was observed for most of the biomarkers analyzed. A preoperative biomarker trial, in which 120 women with breast cancer were treated with either 20 mg or 5 mg or 1 mg/day of TMX for 4 weeks before surgery, confirmed that TMX at low doses retains antiproliferative activity.

Observations on subgroups of patients included in the phase III prevention trials indicate that the combination of HRT and TMX may be synergistic and may reduce the risks related with the use of either agent alone. The combination of TMX with an AI might provide an advantage by decreasing the risk of bone fractures on one side and of ischemic cardiovascular events or of endometrial cancer on the other side.

The combination of low dose TMX and fenretinide, which is synergistic in experimental mammary tumor models, has proven safe and very well tolerated in a phase IIb clinical trial recently conducted in premenopausal women at risk. Trials with combinations of HRT or of an AI with TMX at low dose in healthy women or in women at high breast cancer risk are presently ongoing. Results of these trials will be discussed.

9 Invited

Chemoprevention of breast cancer. What's next?

L. Ford. *National Cancer Institute, Division of Cancer Prevention, Rockville, MD, USA*

The proof of principle that breast cancer can be prevented in women at increased risk for the disease came with the report of the Breast Cancer Prevention Trial (BCPT) with tamoxifen. The reported results of the BCPT in 1998 demonstrated a 49% reduction in invasive breast cancer in women assigned to tamoxifen vs. placebo. A subsequent report in 2005 of the seven year follow-up of BCPT confirmed this result as well as the side effects associated with tamoxifen, i.e. endometrial cancer and vascular events. The Study of Tamoxifen and Raloxifene (STAR) is attempting to provide an alternative to tamoxifen with fewer side effects in high risk postmenopausal women. More recently, aromatase inhibition (AI) with anastrozole has demonstrated superiority over tamoxifen in reducing both breast cancer recurrence and contralateral breast cancer. The logical next step is comparing the superior SERM in STAR to an aromatase inhibitor in high risk postmenopausal women.

However, much remains to be done to adequately address breast cancer prevention. Both the SERMs and AIs act by interfering with the estrogen receptor (ER) or estrogen synthesis and thus reduce only the risk of estrogen receptor positive breast cancer. There is an urgent need to conduct research aimed at preventing ER negative breast cancer and providing additional choices to premenopausal women. Several candidate agents and current investigations will be discussed including COX-2 inhibition, retinoic acid receptor modulation, and EGFR inhibition. Maximizing benefits while minimizing risk is the key factor in any acceptable preventive intervention in high risk women.

10 Invited

the NSABP's second breast cancer prevention study, the STAR trial

L. Wickerham, V. Fourchotte. *NSABP, East Commons Professional Building 5th F1, Pittsburgh, USA*

The Study of Tamoxifen and Raloxifene (STAR), the NSABP's second breast cancer prevention study, is designed to determine if raloxifene is as good as or better than tamoxifen in the prevention of primary breast cancer.

Between July 1999 and November 2004, 19,747 postmenopausal women at increased risk for breast cancer were randomly assigned to receive either tamoxifen (20 mg) or raloxifene (60 mg) daily for 5 years. Breast cancer risk was estimated using a modified Gail model. Factors incorporated into the model include, age, race, reproductive history, previous benign breast biopsies, and number of first-degree female relatives who have had breast cancer. Ten percent of the women in the STAR trial were between 35 and 49 years of age, 50% were 50–59, and 40% were 60+. Their estimated risk of developing breast cancer over the next 5 years varied from 1.67% to over 5%. Seventy-one percent of the women had one or more first-degree female relatives with breast cancer; 9.1% of the women entered had a history of LCIS, and 19.8% had a previous breast biopsy documenting atypical hyperplasia. 51.7% of the participants had undergone a hysterectomy prior to entry.

Final analysis of the trial will begin when a previously determined number of invasive breast cancers has occurred, which is expected in late spring 2006.