



Embargoed for Release:
7:00 a.m. CT, Dec. 8, 2011

Media Contact:
Jeremy Moore
(215) 446-7109
Jeremy.Moore@aacr.org
In San Antonio:
(210) 582-7021

Addition of Trastuzumab May Potentially Equalize Disease-Free Survival Outcomes Among Obese and Normal-Weight Patients

- Obese patients have larger tumors and increased cancer in lymph nodes.
- Obese patients treated with chemotherapy alone had the worst disease-free survival rate.
- Addition of trastuzumab improved survival rates, regardless of body mass index.

SAN ANTONIO — A large, multicenter, randomized study has shown that obese patients with HER2-positive breast cancer have larger tumors, increased lymph node involvement and, when not treated with trastuzumab, poorer long-term outcomes than normal-weight patients.

This is the first time the relationship between obesity and HER2-positive breast cancer has been studied, according to Jennifer A. Crozier, M.D., a medical resident at Mayo Clinic, Jacksonville, who presented the results at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium, held Dec. 6-10, 2011.

“We knew that obesity was a risk factor for breast cancer,” said Crozier. “However, we had not explored the relationship between body mass and how patients respond to treatment and disease-free survival (DFS).”

The study, known as N9831, included 3,017 patients who were initially classified into two categories based on World Health Organization body mass index (BMI) guidelines: normal-weight patients (BMI less than 30) and obese patients (BMI greater than 30). BMI was measured when patients began chemotherapy.

Researchers randomly assigned patients to treatment with only chemotherapy, with chemotherapy and sequential trastuzumab or with chemotherapy and concurrent trastuzumab.

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When data were first examined, there were no significant differences in DFS between obese and normal-weight patients in any arm at three, five and seven years of follow-up. The team then subdivided normal-weight patients to determine if those patients considered overweight, with BMI between 25 and 29, might be affecting the analysis.

They found that obese patients and overweight patients had lower DFS rates of 70.6 percent and 65.9 percent, respectively, after seven years when not treated with trastuzumab compared with a rate of 74.7 percent among normal-weight patients also treated with chemotherapy alone. Results suggested that adding trastuzumab to treatment, particularly when received concurrently with chemotherapy, may potentially equalize DFS rates, with five-year rates of about 85 percent for normal-weight and overweight patients and 82.6 percent for obese patients.

Researchers observed these DFS rates among patients who received concurrent trastuzumab, regardless of BMI. Among patients treated with sequential trastuzumab, normal-weight patients appeared to have benefited more from the treatment than obese patients. Patients treated with chemotherapy alone had the worst observed DFS rate of the three groups, highlighting the potential importance of trastuzumab in treating HER2-positive breast cancer.

The researchers also alleviated the concern that hormonal differences in obese patients might undercut trastuzumab's effectiveness.

“Overall, we can see in the trends that weight management is going to be important in treating HER2-positive breast cancer,” said Crozier. “The next step is to examine how weight management during different stages of treatment affects outcomes.”

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The mission of the CTRC-AACR San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR) and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR's scientific prestige in basic, translational and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. The 34th annual symposium is expected to draw nearly 8,000 participants from more than 90 countries.

Presenter: Jennifer A. Crozier, M.D.

Abstract Number: P2-12-02

Title: Correlation between BMI and Clinical Outcome of Patients with Early Stage HER2+ Breast Cancer from the N9831 Clinical Trial.

Author Block: *Jennifer A Crozier¹, Alvaro Moreno-Aspitia¹, Karla V Ballman², Silvana Martino³, Leila A Kutteh⁴, Nancy E Davidson⁵, Peter A Kaufman⁶ and Edith A Perez¹.* ¹Mayo Clinic, Jacksonville, FL; ²Mayo Clinic, Rochester, MN; ³The Angeles Clinic and Research Institute, Santa Monica, CA; ⁴Oncology Associates at Mercy Medical Center, Cedar Rapids, IA; ⁵University of Pittsburgh Cancer Institute, Pittsburgh, PA and ⁶Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Background: Obesity, as defined by body mass index (BMI), has been associated with increased recurrence rate, shorter DFS and increased death rates due to breast cancer (BC). Most of the studies to date have examined the relationship of BMI and DFS in patients with hormone receptor positive disease. To our knowledge, BMI and its relationship with outcome in early stage HER2 positive breast cancer has not previously been examined. The N9831 is a large phase III trial testing the role of trastuzumab in the adjuvant setting of high risk patients with early stage HER2+ BC. We hypothesized that the occurrence of overweight and obesity may correlate with outcome.

Methods: This analysis presents BMI and its relation to tumor characteristics and DFS in patients (pts) enrolled in the N9831 clinical trial. Pts were categorized as normal weight, overweight or obese using the WHO BMI classification parameters of < 25%, 25-29% and \geq 30% respectively. For patient characteristics, patients were grouped into non-obese (BMI < 30) and obese (\geq 30) cohorts. DFS was estimated by the Kaplan-Meier method. Comparisons between arms A (chemotherapy alone), B (chemotherapy plus sequential trastuzumab) and C (chemotherapy plus concurrent trastuzumab) were performed using the Cox proportional hazards model, stratified by BMI.

Results: Analysis was completed on 3,017 eligible pts. Obese pts were more likely to be older and postmenopausal ($p < 0.0001$ for both). There was no significant association between BMI and ER/PR status ($p = 0.07$) or histologic tumor grade ($p = 0.33$). Obese pts were found to have significantly larger tumors ≥ 2 cm ($p = 0.002$) and more positive lymph nodes ($p = 0.02$). There was no significant difference in DFS within each intrinsic arm (A, B and C) between the obese and non-obese pts at 3, 5 or 7 yrs of follow up. However, pts in the non-obese group had significantly improved DFS in arm B and C compared to arm A ($p = 0.001$ and $p < 0.0001$ respectively). Also obese pts in arm C had significantly improved DFS compared to obese pts in arm A ($p = 0.008$). There was a trend of improved DFS in the obese group in arm B compared to arm A, but this was not statistically significant ($p = 0.09$). Pts in the normal weight and overweight groups did significantly better in arm B ($p = 0.02$ for both) and arm C ($p = 0.01$ and $p = 0.002$ respectively) compared to arm A.

Conclusions: This analysis of data from the N9831 study confirms that obese pts with early stage HER2+ tumors have worse clinical outcome than pts with BMI < 30%. Adjuvant

trastuzumab improved clinical outcome regardless of BMI. This study supports weight loss intervention for obese women with early stage HER2+ BC.