

Trastuzumab in adjuvant therapy for early-stage breast cancer

Current trials indicate that the addition of trastuzumab prolongs disease-free survival

Interim analyses of data from two North American randomized clinical trials^{1,2} and one large international trial³ reported at the 2005 Annual Meeting of the American Society of Clinical Oncology (ASCO) in Orlando, Florida, provide strong support for use of trastuzumab (Herceptin) as adjuvant therapy for early-stage, HER2-positive operable breast cancer.

Adjuvant trastuzumab/paclitaxel therapy

In a combined study population from National Surgical Adjuvant Breast and Bowel Project protocol B-31 (NSABP B-31) and two of the arms of the North Central Cancer Treatment Group protocol N9831 (NCCTG N9831), more than 3,300 women with node-positive or high-risk node-negative disease that was strongly positive (3+) for HER2 on immunohistochemical staining or fluorescence in situ hybridization (FISH) underwent surgery and received chemotherapy with doxorubicin and cyclophosphamide (AC regimen) followed by paclitaxel with or without concurrent trastuzumab therapy (Figure 1). The NCCTG N9831 trial also contained a sequential treatment arm, discussed later in this report, in which patients received

trastuzumab after completing all other chemotherapy that was not included in the combined study analysis. Both studies were launched in 2000 to determine whether the addition of trastuzumab is superior to chemotherapy alone as adjuvant therapy for early-stage resectable breast cancer.

The study design called for early termination of the trial if the interim analysis showed a clear benefit of one treatment strategy over the others at a probability value of 0.0005. This interim analysis reflected findings on 3,351 patients, 1,736 from NSABP

the patients had a normal left ventricular ejection fraction (LVEF) and had no past or active cardiac disease at study entry.

Efficacy

A planned interim analysis of the primary endpoint of disease-free survival (after 355 events) showed that the addition of trastuzumab to paclitaxel following AC chemotherapy among patients with HER2+ disease (6% of whom had high-risk, node-negative disease and 94% node-positive disease) was associated with a

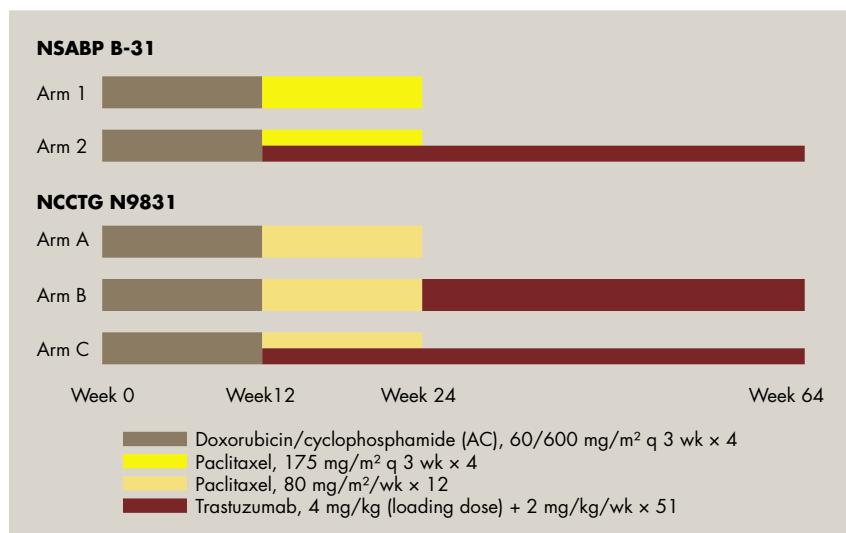


FIGURE 1 Treatment arms in National Surgical Adjuvant Breast and Bowel Project protocol B-31 (NSABP B-31) and North Central Cancer Treatment Group protocol N9831 (NCCTG N9831).

B-31, who had been followed for a median of 2.4 years, and 1,615 from NCCTG N9831, who had been followed for a median of 1.5 years. Approximately half of the women were younger than 50 years of age. All of

significant 52% reduction in the risk of breast cancer recurrence compared with paclitaxel alone over 3 years. The relative risk reduction benefit of concurrent adjuvant trastuzumab and paclitaxel therapy was the same irrespec-

Summary by Matt Stenger, MS; reviewed by Edith A. Perez, MD, Professor of Medicine, Mayo Clinic College of Medicine, and Director of the Clinical Cancer Research Study Unit and Breast Cancer Program, Division of Hematology/Oncology, Mayo Clinic, Jacksonville, FL.

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tive of patient age, hormone receptor status, tumor size, number of positive nodes, or enrollment in either study. Although a relative risk reduction of 52% was also noted in the subset of patients with node-negative disease, there was insufficient statistical power to establish efficacy in this subgroup.

With regard to secondary endpoints, the addition of trastuzumab to adjuvant paclitaxel therapy was associated with a significant 53% reduction in risk for first distant disease recurrence over 3 years, with follow-up thus far indicating a decreasing risk of distant recurrence over time and a significant 33% reduction in risk of mortality over a median follow-up of 2 years (Figure 2). However, the total number of deaths occurring over this short period was too few to establish a significant advantage of combined trastuzumab/paclitaxel therapy over paclitaxel alone on overall survival.

Cardiotoxicity

The combination of adjuvant trastuzumab and chemotherapy was not without risk: Trastuzumab discontinuation due to symptomatic or asymptomatic cardiac dysfunction occurred in 2.1%, 7.7%, 7.2%, and 2.9% of recipients in the NSABP B-31 study population during the first, second, third, and fourth quarters, respectively, of the first year of treatment. Over 3 years, cardiac events occurred in 4.0% of patients receiving adjuvant treatment with trastuzumab plus paclitaxel versus 0.6% of those treated with paclitaxel alone in the NSABP B-31 study, with congestive heart failure (CHF) occurring in 30 patients versus 3 patients and cardiac death occurring in 0 versus 1 patient. LVEF following AC treatment and age were independent predictors of trastuzumab-associated CHF. These data led the investigators to conclude that careful monitoring of cardiac function is vital if trastuzumab is to be used in the adjuvant setting. The joint interim analysis of NSABP B-31 and two of the three arms of NCCTG N9831 did not in-

clude combining cardiotoxicity data. Nine months from study entry, the observed risk of CHF in NCCTG N9831 was between 2.2% and 3.3%. Further follow-up of these patients is awaited.

Concurrent versus sequential trastuzumab

Given the success of adjuvant concurrent trastuzumab/paclitaxel therapy demonstrated in both randomized clinical trials, an unplanned interim analysis was performed in the NCCTG N9831 study (as requested by the Data Monitoring Committee) that compared concurrent therapy with trastuzumab and paclitaxel following surgery and AC chemotherapy with sequential administration of paclitaxel and trastuzumab to provide guidance for optimal management of patients who might receive adjuvant trastuzumab.

Survival benefit

With regard to disease-free survival, sequential use of trastuzumab following adjuvant paclitaxel treatment was associated with a nonsignificant 13% reduction in risk of disease recurrence compared with use of paclitaxel alone, whereas concurrent adjuvant treatment with paclitaxel plus trastuzumab followed by trastuzumab alone was associated with a 36% reduction ($P = 0.011$) in risk of recurrence compared with sequential ther-

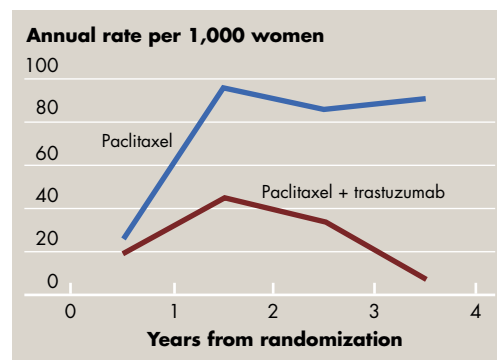


FIGURE 2 Risk for first distant disease recurrence. Adapted, with permission, from Romond et al.¹

apy (Table 1). With regard to overall survival, sequential administration of paclitaxel and trastuzumab produced a nonsignificant 15% reduction in risk of mortality compared with paclitaxel alone; compared with sequential treatment, concurrent paclitaxel/trastuzumab therapy followed by trastuzumab therapy alone produced a nonsignificant 26% reduction in risk of mortality (Table 1).

The investigators concluded that additional follow-up is necessary to determine whether the trend in the difference between concurrent and sequential treatment with regard to disease-free survival will continue and whether the difference in survival observed between sequential and concurrent therapy will become statistically significant with time.

TABLE 1
Three-year disease-free and overall survival: concurrent vs sequential adjuvant treatment with paclitaxel and trastuzumab

Comparison	Hazard ratio	P value
Disease-free survival		
Concurrent vs control*	0.48	< 0.001
Sequential vs control†	0.87	NS
Concurrent vs sequential†	0.64	0.01
Overall survival		
Concurrent vs control*	0.67	< 0.02
Sequential vs control†	0.85	NS
Concurrent vs sequential†	0.74	NS

* From joint NSABP B-31 and NCCTG N9831 interim analysis

† From NCCTG N9831 interim analysis

Adapted, with permission, from Perez et al.

Safety analysis

An analysis of cardiac toxicity after 9 months of treatment—at which point patients receiving concurrent treatment with trastuzumab and paclitaxel would have received 12 more weeks of exposure to trastuzumab than those receiving sequential treatment—showed that the incidence of cardiac events (CHF or cardiac death) was 2.2% greater with sequential treatment versus adjuvant therapy with paclitaxel alone and 3.3% greater with concurrent treatment versus paclitaxel alone.

Other data from the NCCTG N9831 study indicated a modest degree of concordance between local and central laboratories with regard to HER2 testing with both immunohistochemistry (HercepTest, 81%) and FISH (87%) and a high level of agreement between local and central labs for negative results (94.5% for immunohistochemical staining [0, 1+, or 2+] and 95.1% for FISH [gene not amplified]). Accurate HER2 testing was deemed critical by the research team, given the degree of benefit observed with the addition of trastuzumab to adjuvant therapy in HER2+ disease.

Trastuzumab alone as adjuvant therapy

In the HERA (HERceptin Adjuvant) trial, conducted at 478 sites in 39 countries, more than 5,000 women with node-positive or high-risk node-negative disease that was strongly HER2+ (as shown by FISH or 3+ immunohistochemical staining) were randomized to receive 1 or 2 years of adjuvant treatment with trastuzumab (8 mg/kg followed by 6 mg/kg once every 3 weeks) or observation after surgery and completion of at least four cycles of (neo)adjuvant therapy with or without radiation therapy. Patients had to have LVEF \geq 55% for entry. Screening of patients for entry into the HERA trial was started in December 2001 and ended in May 2004.

Initial data are available from the comparison of 1 year of trastuzumab

treatment versus observation, involving more than 3,300 patients followed for a median of 1 year (ie, a shorter period than the follow-up period in the joint analysis of NSABP B-31 and NCCTG N9831). More than 68% of patients had received adjuvant chemotherapy with anthracyclines and 26% with taxanes plus anthracyclines.

Grade 3 or 4 adverse events occurred in 4.3% of the observation group ($n = 1,736$) versus 7.9% of the 1-year trastuzumab group ($n = 1,677$), serious adverse events occurred in 4.7% versus 7.0%, and fatal adverse events occurred in three patients (0.2%) versus six patients (0.4%); 8.5% of the patients receiving trastuzumab were withdrawn from treatment. With regard to cardiac toxicity, a decrease in LVEF of ≥ 10 points to $< 50\%$ occurred in 2.2% of the observation group versus 7.1% of the trastuzumab group, LVEF dysfunction to the same degree plus symptomatic CHF occurred in 0% versus 0.5%, and cardiac death occurred in 0.1% versus 0%.

With regard to the primary endpoint of disease-free survival, trastuzumab treatment was associated with a 46% reduction in risk of recurrence ($P < 0.0001$). This benefit was largely independent of nodal status, hormone receptor status, age, and type of (neo)adjuvant chemotherapy. For the secondary endpoints of relapse-free survival, distant disease-free survival, and overall survival, trastuzumab treatment was associated with a 50% reduction in risk of relapse ($P < 0.0001$), a 49% reduction in risk of distant metastases ($P < 0.0001$), and a nonsignificant 24% reduction in risk of mortality at 2 years. Although 33% of patients in the HERA trial had node-negative disease, 2-year disease-free survival in both the control and the trastuzumab arm was approximately 9% lower than that observed in the North American trials. Whether differences in chemotherapy administration may have played

a role is a matter of investigation, as only 26% of patients received concurrent adjuvant anthracycline/taxane therapy in HERA, versus 100% of the patients enrolled in NSABP B-31 and NCCTG N9831.

The initial results of this large-scale, phase III multicenter trial—although drawn from a different population of patients than those participating in NSABP B-31 and NCCTG N9831 in that all chemotherapy and radiotherapy had to be completed before enrollment—thus support the interim findings from the two North American studies, namely, that adjuvant therapy with trastuzumab prolongs disease-free survival and reduces the risk of distant metastases and death in women with early-stage resectable HER2+ breast cancer, but they also highlight the importance of accurate HER2 testing and long-term monitoring of cardiac function.

Although adjuvant treatment with trastuzumab was associated with a low incidence of symptomatic CHF in the HERA trial, the investigators concluded that longer follow-up is needed to better quantify the risk, and all patients enrolled in the trial continue to be followed for long-term safety. Results regarding the optimal duration of adjuvant trastuzumab therapy (1 or 2 years) will be available in 2008.

References

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