

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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## New Developments in Adjuvant Therapy for Breast Cancer

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### **H&O** Historically, what has been the approach to adjuvant therapy for breast cancer?

**GS** For at least the past 20 years, we have known that adjuvant systemic therapy reduces the risk of recurrence and death for patients with early-stage breast cancer. Until very recently, adjuvant therapy fell into 2 general categories: hormonal therapy and chemotherapy. Hormonal therapy has typically been given to patients with tumors that are estrogen receptor (ER)-positive. Chemotherapy has typically been given to both ER(+) and ER(-) patients, most often those with more aggressive tumors.

In the last year or so, changes in the approach to adjuvant therapy have involved the segmenting of the breast cancer population into different subgroups for which particular therapies are most likely to be beneficial. Patients are categorized according to ER and human estrogen receptor (HER)-2 status, and other biologic parameters are now becoming apparent.

### **H&O** What are these new biologic parameters?

**GS** This line of research began with the identification of ER-sensitive tumors in the late 1960s. Beginning in the late 1970s and for the subsequent 20 years, investigators evaluated the efficacy of hormonal therapy for ER(+) patients with the selective ER-modulator tamoxifen. Until very recently, tamoxifen represented the standard of care for ER(+) patients.

More recently, tamoxifen has been gradually replaced by aromatase inhibitors such as exemestane (Aromasin, Pfizer), letrozole (Femara, Novartis), and anastrozole (Arimidex, AstraZeneca). These 3 agents have been evalu-

ated in early-stage breast cancer and each appears to be somewhat better than tamoxifen in terms of preventing recurrence in these patients.

The HER2(+) population represents another important subgroup of early-stage breast cancer patients. We have known for some time that HER2 positivity is associated with a poor prognosis for patients with early-stage breast cancer, and that treating patients based on HER2 status in the setting of advanced or metastatic disease can improve survival. However, in the last few months, it has become apparent that targeting HER2 in the adjuvant setting can improve relapse-free and overall survival.

### **H&O** Could you describe the studies of HER2-targeted adjuvant therapy in early-stage breast cancer?

**GS** Two North American trials were reported in a joint analysis presented at the 2005 annual meeting of the American Society of Clinical Oncology (ASCO): the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B31 and the Breast Cancer Intergroup trial N9831. In these studies, patients were randomized to receive chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab (Herceptin, Genentech). These studies produced dramatic and compelling evidence suggesting that trastuzumab markedly improves relapse-free survival in the first few years after diagnosis. [This report was presented in the scientific symposium "Advances in Monoclonal Antibody Therapy for Breast Cancer" and is accessible on-line at the Virtual Meetings section of the ASCO web site, [www.asco.org](http://www.asco.org). There is no published abstract for this joint analysis.]

The hazard ratio (HR) for the primary endpoint of the trial, relapse-free survival, was 0.48; in other words, the trastuzumab-containing arm was associated with a 52% reduction in the odds of recurrence. In addition, overall survival was statistically significantly longer for this treatment arm, with an HR of 0.67.

The European HERA trial, results of which were presented at the 2005 ASCO annual meeting by Dr. Martine Piccart, also evaluated the addition of trastuzumab to adjuvant therapy for early-stage HER2(+) breast cancer. In this study, all patients received upfront chemotherapy and were then randomized to receive additional chemotherapy with or without trastuzumab. As in the US trials, the results were strikingly positive in favor of trastuzumab, with an HR of 0.55 for relapse-free survival. The median follow-up with this trial was quite short at the time of the report, and no statistically significant improvement in overall survival had yet been observed; however, this difference is expected to emerge with longer follow-up.

In addition to the 2 North American trials, both of which provide solid evidence that trastuzumab should be part of the standard of care for patients with HER2(+) early-stage breast cancer, the North Central Cancer Treatment Group reported a substudy of N9831 in which patients were randomized to receive chemotherapy followed by trastuzumab, similar to the HERA trial. An early report of this trial, presented by Dr. Edith Perez at the 2005 ASCO annual meeting, suggested that trastuzumab administered alongside chemotherapy rather than afterward is associated with improved outcomes. This finding suggests synergistic activity between chemotherapy and trastuzumab, which has already been demonstrated in preclinical models.

Another study, Breast Cancer International Research Group (BCIRG) 006, not presented at the 2005 ASCO annual meeting but scheduled for presentation at the San Antonio Breast Cancer Symposium in December 2005, evaluated adjuvant therapy with a non-anthracycline-based chemotherapy regimen—carboplatin plus docetaxel—plus trastuzumab compared with doxorubicin/cyclophosphamide followed by paclitaxel with or without trastuzumab. This study is important because one of the major findings in the joint analysis was a 3–4% incidence of congestive heart failure among patients receiving docetaxel/cyclophosphamide followed by paclitaxel/trastuzumab. An analysis presented at the ASCO meeting by Dr. Dennis Slamon suggested that the combination of carboplatin/paclitaxel/trastuzumab might carry a lower risk of cardiotoxicity. If these regimens prove to be equally efficacious, then the non-anthracycline-containing regimen might be an appropriate replacement or alternative to doxorubicin/cyclophosphamide followed by paclitaxel/trastuzumab.

## **H&O** Did any further patient subdivisions show a propensity for response?

**GS** In both the HERA trial and the combined NSABP-B31 and N9831 studies, a Forrest plot was used to analyze the data in terms of nodal status, tumor size, age, menopausal status, and other parameters. The risk reductions were equivalent across all subgroups. Thus, it appears that HER2 positivity is the driving force behind therapeutic benefit, regardless of other characteristics of the patient or the disease.

## **H&O** What are the next steps in advancing adjuvant therapy for breast cancer?

**GS** The first issue to be addressed is regarding cardiotoxicity. An analysis by Dr. Ed Romond found that some subgroups of NSABP-B31 and N9831 had an excessive risk of congestive heart failure associated with doxorubicin/cyclophosphamide followed by paclitaxel/trastuzumab. Among patients over age 50 with a starting left ventricular ejection fraction of 50–55%, 19% developed congestive heart failure. This finding leads one to ask whether this regimen is appropriate for these patients. In the near future, data from the BCIRG 006 study will hopefully answer this question.

Another area of research involves subgroups. The vast majority of patients in the joint analysis were lymph node-positive. In the HERA trial, approximately one third of patients were lymph node-negative. While the initial data suggest that a similar proportional improvement is associated with trastuzumab-containing adjuvant therapy for all patients, questions remain. For example should a patient with T1c, lymph node-negative, ER(+), HER2(+) breast cancer receive adjuvant chemotherapy? Such patients likely need adjuvant trastuzumab, but whether or not this should be given with chemotherapy is not clear. The follow-up with the HERA trial has not been long enough to provide a clear sense of which low-risk subgroups clearly require adjuvant trastuzumab.

In addition, further studies of the data from the joint analysis and the HERA trial will hopefully elucidate the mechanisms of trastuzumab resistance. Tissue was collected in these trials and now genomic and immunohistochemical analyses can be performed in order to see what factors correlate with failure or benefit. Based on these findings, new strategies for overcoming resistance may be identified.

Finally, the HERA trial also evaluated duration of therapy by randomizing patients to receive 1 or 2 years of therapy. The results of this arm of the trial are expected soon and should provide important information regarding whether duration is a factor in patient outcome. Right now, 1 year of therapy is the standard approach.

**H&O** Will studies evaluate trastuzumab combined with other novel biologic agents in the adjuvant setting?

**GS** Yes. While the dramatic reductions in the risk of recurrence demonstrated in the joint analysis and the HERA trial are obviously impressive, there is still a significant portion of the patient population not benefitting. We need to find ways to improve this outcome even further. Such improvements will likely entail combining trastuzumab with other novel agents. Drugs that target

HER2 downstream of the activity of trastuzumab are good candidates for combination therapy. A randomized trial of trastuzumab with or without lapatinib (Glaxo-SmithKline) in the adjuvant setting is in the planning stages. Investigators are also considering combining trastuzumab with an antiangiogenic agent such as bevacizumab (Avastin, Genentech).

### Suggested Reading

Kudachadkar R, O'Regan RM. Aromatase inhibitors as adjuvant therapy for postmenopausal patients with early stage breast cancer. *CA Cancer J Clin.* 2005;55:145-163.

Gradishar WJ. Safety considerations of adjuvant therapy in early breast cancer in postmenopausal women. *Oncology.* 2005;69:1-9.

Jones KL, Buzdar AU. A review of adjuvant hormonal therapy in breast cancer. *Endocr Relat Cancer.* 2004;11:391-406.

The joint analysis of NSABP-B31 and N9831 and the HERA study are currently under editorial review at the *New England Journal of Medicine.*



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