

EDITORIALS



Trastuzumab in the Treatment of Breast Cancer

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Two articles in this issue of the *Journal* report on the considerable therapeutic benefit of trastuzumab, a monoclonal antibody, in primary breast cancer, as measured by reductions in the rates of both recurrence and death.^{1,2} These reports, which complete the bench-to-bedside cycle, are elegant examples of translational research. The human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGFR) family of transmembrane tyrosine kinases and is normally involved in the regulation of cell proliferation. The *HER2* gene, located on the short arm of chromosome 17, was discovered and cloned in 1983 and found to be related to, albeit distinct from, the EGFR.³ Amplification (an excess number of gene copies) or overexpression (excess production of protein) confers on the affected cancer cell aggressive behavioral traits, including enhanced growth and proliferation, increased invasive and metastatic capability, and stimulation of angiogenesis.

Patients with breast cancer in which *HER2* is amplified or *HER2* is overexpressed are likely to have poorly differentiated tumors with a high proliferative rate, positive axillary lymph nodes, and decreased expression of estrogen and progesterone receptors. These characteristics are associated with an increased risk of disease recurrence and death.⁴ The observation by Sato et al. that a monoclonal antibody against the EGFR inhibited binding of the natural ligand (EGF) to the receptor and inhibited receptor phosphorylation and signaling⁵ encouraged scientists at Genentech to develop a mouse monoclonal antibody with high affinity for the extracellular domain of the *HER2* transmembrane protein. The humanized version of this antibody is trastuzumab — a molecularly engineered antibody that was produced by inserting portions of the antigen-binding site of the murine antibody into a human monoclonal antibody.⁶

Over the ensuing decade, trastuzumab was found to produce objective regressions in 11 to 26 percent of patients with metastatic disease without undue toxic effects. Patients who had tumors in which *HER2* amplification was detected by fluorescence in situ hybridization (FISH) (thus, FISH-positive tumors) or tumors that showed overexpression of *HER2* (a result on immunohistochemical analysis of 3+) had a response rate of 34 percent after treatment with trastuzumab alone.

Trastuzumab combined with cytotoxic agents commonly used in the management of metastatic breast cancer, especially taxanes, vinorelbine, and platinum salts, also gave encouraging results. Preclinical studies had suggested that substantial additive and sometimes synergistic effects could be expected from these combinations.⁷ These rationally developed trastuzumab combinations were taken to clinical trials. Two phase 3 trials compared first-line chemotherapy alone with the combination of chemotherapy with trastuzumab in patients with *HER2* overexpression in metastatic breast cancer. In the trastuzumab group there was a dramatic improvement in all therapeutic end points — time to progression, response rate, duration of response, and survival.^{8,9} An unexpected observation in these phase 3 trials was the development of congestive heart failure in 2 to 16 percent of the patients who were treated with trastuzumab and chemotherapy; the frequency was highest among patients receiving anthracycline and trastuzumab simultaneously.⁸ The addition of platinum salts significantly enhanced the efficacy of the taxane–trastuzumab doublet, and this triple-drug combination provides optimal palliation to patients with *HER2*-positive metastatic breast cancer.¹⁰

The adverse prognosis of *HER2*-positive breast cancer led to the development of clinical trials to assess the efficacy and safety of trastuzumab in pa-

tients with primary breast cancer. Although there was concern about the possibility of inducing long-term cardiac dysfunction with this agent, experience in the metastatic setting suggested that cardiac dysfunction was potentially reversible. Because of the high risk of recurrence and death in HER2-positive breast cancer, a rate of congestive heart failure of no more than 4 percent above that without trastuzumab was considered acceptable.

Four large multicenter trials were designed to test the role of trastuzumab as adjuvant therapy after surgical treatment of primary breast cancer. The results of three of these trials (the combined results of the National Surgical Adjuvant Breast and Bowel Project trial [B-31] and the North Central Cancer Treatment Group trial [N9831] and those of the Herceptin Adjuvant [HERA] trial) are reported in this issue of the *Journal*.^{1,2} The results are simply stunning. With very brief follow-up (one to two and a half years), all three trials show highly significant reductions in the risk of recurrence, of a magnitude seldom observed in oncology trials. In fact, only tamoxifen administered for five years to patients with estrogen-receptor-positive primary breast cancer produces a 50 percent reduction in the risk of recurrence. Many recent phase 3 trials of adjuvant systemic therapy for breast cancer highlighted absolute benefits of 2 to 6 percent after four to six years of follow-up. In contrast, an absolute difference of 6 percent is evident in the HERA trial at two years, with a benefit of 8 percent observed in the joint analysis of the trials B-31 and N9831 during the same interval; by four years, these two trials project an absolute benefit of 18 percent, exceeding all previously reported therapeutic benefits in breast cancer.

Survival differences are also emerging from these comparisons. The most dramatic observation in these trials, however, is the comparison of hazard ratios in the joint analysis: the initial peak in recurrences that is generally expected during the first two to three years, and indeed, was observed in the control groups of the two trials, has been abrogated by trastuzumab, and the hazard ratio remains very low even a year after completion of trastuzumab therapy. This observation suggests a dramatic and perhaps permanent perturbation of the natural history of the disease, maybe even a cure. Longer follow-up will determine whether this interpretation is correct.

These results compelled the respective data and safety monitoring committees to stop the trials after the first interim analyses. Trastuzumab was of-

fered to all patients in the control groups. These modifications were clearly appropriate, although they will cloud subsequent analyses and probably result in underestimation of the overall benefit of trastuzumab therapy.

On the basis of these results, our care of patients with HER2-positive breast cancer must change today. Certainly, patients with lymph-node-positive, HER2-positive breast cancer should receive trastuzumab as part of optimal adjuvant systemic therapy, unless the antibody is clearly contraindicated. Patients with negative lymph nodes, whose estimated risk of recurrence after optimal chemotherapy and endocrine therapy comfortably exceeds the risk of the cardiac toxic effects of trastuzumab, should also be offered the antibody. Since most HER2-positive tumors have other adverse prognostic factors, this risk-benefit scenario is likely to apply to many patients with node-negative breast cancer.

Although these trials provide some answers, they also raise many new questions. What is the optimal schedule for therapy with trastuzumab: should it be given simultaneously with or sequentially after chemotherapy? Comparison of trials B-31 and N9831 and the HERA trial suggests that cardiotoxicity is lower after sequential administration. However, we cannot rule out the possibility that simultaneous administration of chemotherapy and trastuzumab is more effective than sequential administration. Preclinical experiments indicate that simultaneous administration is critical to optimal cytotoxic effect, whereas sequential administration results in cytostasis.¹¹ Longer follow-up of the HERA trial and trial N9831 will confirm or refute these preclinical results. If they are confirmed, it may follow that continuation of trastuzumab beyond the completion of chemotherapy is unnecessary — a concept to be tested in future trials.

Although the major results presented in these two reports appear to be identical, there are important differences between the reports that deserve highlighting and that may provide clues to future developments. One third of patients included in the HERA trial had lymph-node-negative breast cancer. This would indicate a better overall prognosis for this patient population. However, the disease-free survival curves of the two reports indicate that both the control group and the trastuzumab group of the combined North American report fared better than the corresponding groups in the HERA trial. It is tempting to hypothesize that this difference is partly explained by differences in the schedule of admin-

istration and in the adjuvant chemotherapy regimens used: only 26 percent of the patients in the HERA trial received a taxane, whereas all patients in the combined analysis received paclitaxel.

There are other important questions that can be answered with longer follow-up in these two trials and in future trials. What is the nature and reversibility of cardiac dysfunction? The joint analysis provides reassuring but very preliminary information about symptomatic control of heart failure in the majority of patients. What will be the long-term effects of even treatable congestive heart failure? Will cardiac function normalize in the absence of cardiac medication? Even with the large therapeutic benefits of trastuzumab, avoiding unnecessary toxic effects is an important goal. Assessing the worth of including a group that does not receive anthracyclines, as in another trial (Breast Cancer International Research Group trial 006), will be of critical importance to the design of the next generation of adjuvant trials with trastuzumab.

Clearly, the results reported in this issue of the *Journal* are not evolutionary but revolutionary. The rational development of molecularly targeted therapies points the direction toward continued improvement in breast cancer therapy. Other targets and other agents will follow. However, trastuzumab and the two reports in this issue will completely alter our approach to the treatment of breast cancer.

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Acute Lung Injury — Affecting Many Lives

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Acute lung injury is the clinical syndrome of rapid-onset bilateral pulmonary infiltrates and hypoxemia of noncardiac origin. When the hypoxemia is severe, the condition is termed the acute respiratory distress syndrome (ARDS).¹ As archetypal examples of critical illness requiring intensive care, advanced life support, and considerable health care resources, acute lung injury and ARDS have attracted substantial research interest. An extensive body of laboratory and clinical investigation has been amassed since the original description almost 40 years ago, cataloguing our advancing knowledge of the cause, pathophysiology, and management of these complex and often lethal syndromes. However, estimates of their incidence have varied wide-

ly,²⁻⁵ and the true magnitude of these syndromes — and the implications for health care delivery — have been unclear.

In this issue of the *Journal*, Rubenfeld and colleagues report the results of the first large prospective study of the incidence of and mortality associated with acute lung injury and ARDS in the United States.⁶ On the basis of a one-year prospective evaluation of all cases of acute lung injury and ARDS managed in all the adult intensive care units (ICUs) of King County, Washington, the authors generated national estimates of 86 cases per 100,000, or almost 200,000 cases per year, with an in-hospital mortality of 38.5 percent. They exploited the natural and political boundaries around King County to