HERe-2 Stay: The Continuing Importance of Translational Research in Breast Cancer

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This issue of the Journal contains two important articles that discuss human epidermal growth factor receptor 2 (HER2), also known as c-erbB2 or neu, as a therapeutic target in breast cancer (1,2). The first details preclinical studies that examine the combination of trastuzumab with a number of chemotherapeutic agents. The second applies the knowledge learned in the preclinical studies to the clinical setting and the treatment of patients with HER2-positive metastatic breast cancer. These studies are important with regard to what they tell us about HER2-positive breast cancer and its treatment and about a style of research. All have important implications.

HER2 is a member of a family of transmembrane receptor tyrosine kinases. To summarize more than two decades of research, HER2 lacks a functioning ligand-binding domain yet represents the preferred dimerization partner for other members of the EGFR family (3,4). Since the late 1980s, HER2 has been known to be overexpressed in the tumors of approximately 20% of patients with breast cancer. Overexpression is typically a consequence of amplification at the DNA level (measurable in the clinic by fluorescence in situ hybridization [FISH]) and is associated with an increased risk of relapse and death for patients with early-stage breast cancer (5). The poor prognosis is the clinical manifestation of the many biologic actions of HER2: increased proliferation, increased cell survival, increased invasion and metastasis, and increased angiogenic activity (6,7).

In addition, amplification of HER2 results in impaired response to hormonal manipulations through cross-talk with the estrogen receptor complex (8,9). Although not the subject of this editorial, co-blockade of the estrogen receptor and of either HER2 or EGFR is currently being tested in clinical trials as a potential means of abrogating or preventing hormonal resistance. Similarly, given the role of HER2 as an upstream regulator of vascular endothelial growth factor (VEGF), co-blockade of HER2 and VEGF is also currently under exploration in clinical trials (10).

Recognition of the clinical importance of HER2 in breast cancer led to the development in the 1990s of agents that target HER2, in particular, to the development of the humanized monoclonal antibody trastuzumab. In 1998, trastuzumab was approved by the U.S. Food and Drug Administration for clinical use largely on the basis of a randomized clinical trial (11) that compared chemotherapy to chemotherapy plus trastuzumab as a front-line treatment for patients with metastatic breast cancer. This randomized trial demonstrated unequivocally that the addition of trastuzumab to chemotherapy with either doxorubicin plus cyclophosphamide or paclitaxel resulted in increased survival for women with HER2-positive metastatic breast cancer (11).

The introduction of any new agent into the breast cancer arena is typically followed by a “feeding frenzy” in which clinical trialists scurry to combine the new agent with existing agents. Such “toothpaste A + toothpaste B” combinations litter the medical literature, rarely have any biologic basis, and arguably retard rather than propel the rational development of the new agent. Empiric combination therapy has specific perils beyond mere wastefulness. Indeed, as the HER2 story demonstrates, the combination of trastuzumab with doxorubicin-based chemotherapy was associated with an unacceptably heightened risk of congestive cardiomyopathy (11). This interaction, not detected in initial preclinical toxicology studies, was later found to have a sound biologic basis. HER2 proved to have an important anti-apoptotic role for normal cardiac myocytes, interruption of which leads to increased stress-related cardiac damage (12).

This is where the first article by Pegram et al. (1) in this issue of the Journal comes in. At UCLA, Pegram et al. (1) carefully analyzed the combination of trastuzumab with numerous chemotherapeutic agents, using multiple drug effect/combination index isobologram analysis. This approach allows for the demonstration of synergy in the preclinical setting and, as applied in their study, demonstrated synergy in an in vitro model for the two-drug combinations of trastuzumab with carboplatin, 4-hydroxycyclophosphamide (the active metabolite of cyclophosphamide), docetaxel, or vinorelbine.

Of these four synergistic compounds, carboplatin was of particular interest. The same authors had previously demonstrated a synergistic interaction between cisplatin and the murine precursor of trastuzumab 4D5 (13). Platinating agents have known single-agent activity in metastatic breast cancer (14–16), combine readily with taxanes (17), and lack the cardiotoxic effects of anthracyclines. Previous work (18) demonstrated that antibodies to the HER2/neu receptor block DNA repair after exposure to cisplatin in HER2-positive human breast cancer cells. Pegram et al. (1) similarly now demonstrate that trastuzumab markedly reduces unscheduled DNA synthesis (a marker of DNA repair) in carboplatin-treated HER2-positive SK-BR-3 breast cancer cells. In addition, they show that the combination of carboplatin with docetaxel was markedly synergistic in the combination index analysis.

These in vitro studies led directly to two human in vivo studies, one performed by the Breast Cancer International Research Group (BCIRG) and the other by the UCLA Oncology Research Network (UCLA-ORN) (2). The former trial combined...
cisplatin and docetaxel with trastuzumab, and the latter substituted carboplatin for cisplatin. The results of these two trials are reported together in the second of the two articles by Pegram et al. in this issue of the Journal (2). Both trials represent reasonably well-powered phase II studies—each contained 62 patients—performed in relatively homogenous populations of patients receiving initial chemotherapy for metastatic breast cancer. Both trials initially allowed accrual of patients on the basis of HER2 expression determined by immunohistochemistry, a testing approach with real limitations (19). Because a substantial fraction of tumors tested with immunohistochemistry proved to be HER2-negative by FISH, these trials essentially contain their own HER2-negative internal controls.

From an efficacy standpoint, response rates in both trials suggested that the combination of a platinating agent (either carboplatin or cisplatin) with docetaxel and trastuzumab represents an active regimen in women with front-line HER2-positive disease. Overall response rates were somewhat higher for the cisplatin-based regimen (79%) than for the carboplatin-based regimen (58%). One should not make too much of such differences: it is dangerous to worship at the altar of response rate. This is particularly true, given that response rates for patients with HER2-positive and HER2-negative cancers were virtually identical in the BCIRG trial (2).

Does this clinical experience support the preclinical evidence of synergy? In the clinical setting, synergy is remarkably difficult to prove, particularly in the absence of a randomized, controlled trial design. Certainly the response rates for the three-drug combinations are in the general range seen with platinum-taxane combinations in the absence of trastuzumab. However, I find the median time to progression results observed in these trials (2) to be provocative: 12.7 months for patients with FISH-positive tumors in the BCIRG trial and 15.6 months for patients with FISH-positive tumors in the UCLA-ORN trial. In both trials, the median time to progression was lower for patients with FISH-negative tumors (7.9 and 7.4 months for the BCIRG and UCLA-ORN trials, respectively) than for patients with FISH-positive tumors.

Still, a phase II trial is a phase II trial: a first peek at activity, rather than proof-of-concept. In the long run, response rate and time to progression are, at best, surrogate markers of true clinical benefit. Fortunately, the preclinical and clinical activity reported in these two studies (1,2) paved the way for two important randomized phase III trials. The first of these, a front-line metastatic trial performed by the US Oncology Group, was presented at the 2002 San Antonio Breast Cancer Symposium (20). This trial, to date, reported only in abstract, showed a statistically significantly longer median time to progression for a three-drug combination (carboplatin plus paclitaxel plus trastuzumab) than for the standard two-drug combination (paclitaxel plus trastuzumab). As one might predict, the results were most encouraging for patients with FISH-positive tumors [similar to the phase II results reported by Pegram et al. (2)].

The adjuvant setting represents the next major test of this combination. Several large adjuvant trastuzumab trials are ongoing on a worldwide basis (21). The BCIRG, following up on the data reported in this issue of the Journal, has finished accrual to a large phase III trial, one arm of which represents a platinum-taxanes-trastuzumab combination. The results of this trial are eagerly awaited, as are the results of several other large adjuvant trials targeting HER2.

Nevertheless, the articles by Pegram et al. (1,2) in this issue of the Journal represent an impressive example of translational research at its best. Translational research—that precarious bridge between the laboratory and the clinic—is, in Shakespeare’s words, a “custom more honored in the breach than in the observance.” Clinical researchers are frequently skeptical of laboratory models as a guide to clinical research. “Anybody can cure cancer in a mouse” is a common refrain. Study sections populated by laboratory scientists, by contrast, often judge such work to be “mere phenomenology,” “nonmechanistic,” or a “fishing expedition.”

Pegram et al. (1,2) demonstrate how translational research should be performed, and why. In vitro studies should examine multiple cell lines with the relevant biology rather than just one cell line. The agents examined should be relevant to the disease state (in this case, metastatic breast cancer). The drug concentrations for the agents examined should be clinically relevant. In vivo preclinical animal models should, if at all possible, have been validated through previous work. Observed phenomena (in this case, the synergistic activity of platinating agents when combined with trastuzumab) should be pursued with mechanistic studies (for example, in DNA repair studies). The clinical trials developed from such in vitro and in vivo preclinical research should build on prior trial data (e.g., the prior experience with platinum-taxane combinations), should involve prospective collection of tissues for subsequent biologic analysis, and should be sufficiently well-powered to provide a decent clinical signal. If possible, parallel trials should demonstrate reproducibility of results. All of these criteria were met by Pegram et al. (1,2).

As to why such translational research should be performed, the studies by Pegram et al. also offer a ready answer. Preclinical studies and metastatic phase II trials rarely lead to anything useful for patients: they are wasteful in a profound and disturbing sense, far beyond the inherent messiness of science. I suspect this reflects an inherent lack of vision on the part of both laboratory and clinical researchers. Designing a sequential series of experiments, both laboratory and clinical, that lead intentionally to proof-of-concept adjuvant trials is all too rare. But, as Pegram et al. remind us, it is not impossible.

REFERENCES


