Biologic Approaches to Managing Advanced Breast Cancer

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Introduction

An entirely new spectrum of biologic agents has followed directly from an increased understanding of growth regulatory pathways in eukaryotic cells. Currently, about 100 critical genes in growth stimulatory pathways have been identified as potential targets for development as therapeutic agents. HER2 is a member of a class of molecules in this pathway, called growth factor receptors. Named for “human epidermal growth factor receptor-2” (CRPB-2 or neu), HER2 has a profound significance on metastatic breast cancer. In a state of overexpression, its impact extends from its tumorigenicity, metastatic potential, effects on hormone dependence, and effects on response to tamoxifen and chemotherapy. As a predictor of response to therapy, HER2 expression developed as an aid in the selection of therapy.

Following the humanization of the anti-HER2 antibody, trastuzumab was developed and has promise as an important new agent for the treatment of advanced breast cancer.

HER2 Alteration in Breast Cancer

Following discovery of the HER2 probe in 1987, it was determined that 25% to 30% of women with breast cancer have amplification of this gene. Although expression does not always follow gene amplification, HER2 expression was found to directly correlate to its degree of amplification, such that amplification results in overexpression in 95% of cases.

When HER2 overexpression occurs — at some point between premalignant and preinvasive disease — it affects both the biologic life of the tumor and the prognosis of the patient. In this study, in HER2-normal cases, median survival from the first diagnosis was six to seven years in contrast to three years for patients who overexpressed HER2.

Subsequent to the publication of these results, the literature remained inconclusive for the better part of six years. Today, much of the controversy has been resolved thanks in part to consistent and reliable antibody reagents and technologies such as fluorescence in situ hybridization for detecting the presence of HER2. Currently, HER2 appears to be an independent prognostic factor in node-positive disease and may be predictive in node-negative disease.

The HER2 alteration does not appear to change over time. When it is amplified in the primary tumor, the degree of amplification seems to hold steady throughout the course of disease and is similarly amplified in subsequent metastases.

HER2 Role in Pathogenesis

Basic science studies to determine whether HER2 amplification had a role in pathogenesis, in addition to serving as a prognostic factor correlating to outcome, resulted in finding that the HER2 induces cells toward more aggressive behavior. In laboratory studies, introduction of the HER2 alteration increased the ability of animal to form tumors and markedly boosted the metastatic potential of those tumors.

HER2 and Response to Therapy (Tamoxifen and Chemotherapy)

The biologic effects of HER2 amplification and overexpression extend to effects on hormone dependence and response to therapy. Clinical literature notes that more than half of the women who are HER2-positive are ER/PR-negative. However, women who are HER2-positive and ER/PR-positive may not respond to tamoxifen.

The HER2 alteration has also been shown to affect response to chemotherapy. Retrospective analyses of HER2-positive women who were treated with CMF indicated that they did not respond as well as patients who were HER2 normal, leading investigators to question if HER2 may in fact be causing chemoresistance. Although that finding was confirmed in a large study, there was no decrement in the effectiveness of CMF in HER2 overexpressers in the original Milan CMF vs placebo adjuvant trial for node-positive breast cancer (P. Valagussa, personal communication, April 1999).

The CALGB protocol 8541 indicates that the dose intensity of anthracycline may be important since HER2-positive women treated with 60 mg/m² rather than 30 mg/m² responded better. The NSABP B-11 protocol finds that anthracycline-based therapy produces longer disease-free survival but not overall survival in HER2-positive patients than in HER2-negative patients.

Some investigators have inferred from these data that HER2 positivity may confer a unique, intrinsic sensitivity to anthracycline. Our group has looked directly at the effects of HER2 overexpression on intrinsic drug sensitivity and resistance in breast cancers. We found no significant difference in response to chemotherapy for HER2 normal expressers vs HER2 overexpressers in all seven classes of chemotherapeutic drugs. This result does not imply a contradiction of the results of the NSABP and CALGB studies, but rather a suggestion that HER2 may confer a growth advantage to these tumors.

Trastuzumab

From the enlarged database of knowledge about HER2, investigators moved rapidly into development of a new agent. Phase I studies of anti-HER2 monoclonal antibodies first established its safety and localization to the tumor. Testing of the antiserum antibody led to humanization of the antibody, which then became the drug trastuzumab. At UCLA, the agent was studied alone and in combination and was found to be active. In phase II studies with a larger cohort of metastatic patients who had failed all prior therapy, trastuzumab as a single agent yielded a 12% objective response rate after two or more prior chemotherapy regimens. Consistent with the preclinical data, study patients achieved an objective response rate of 24% when the antibody was used in combination with cisplatin.
In the pivotal trial of trastuzumab in combination with chemotherapy for patients with metastatic disease, the primary endpoints were
time to disease progression and safety. Secondary endpoints included overall response rate, response duration, time to treatment
failure, one-year survival, and quality of life. Survival data for more than two years are now available.

Eligibility for the trial required first-line metastatic breast cancer, HER2 overexpression was determined by immunohistochemistry, no
prior chemotherapy for stage IV disease, measurable disease, and a Karnofsky Performance Status score of 60% or greater.
Stratification to chemotherapy was assigned using the best available chemotherapy in 1995, with patients assigned according to either
prior use or no prior use of anthracyclines. Patients who had not received prior anthracyclines received doxorubicin at 60 mg/m² or
epirubicin at 75 mg/m² plus cyclophosphamide at 600 mg/m² every three weeks for six cycles. Patients who had received prior
anthracyclines were randomized to receive paclitaxel at 175 mg/m² every three weeks plus or minus trastuzumab.

Of 469 patients who were enrolled, 235 were randomized to trastuzumab plus chemotherapy and 234 were randomized to receive
chemotherapy alone. As shown in Table 1, the overall response rate ranged from 43% (anthracycline) to 52% (trastuzumab plus
anthracycline). In the paclitaxel subgroup, the overall response ranged from 16% with paclitaxel alone to 42% with trastuzumab plus
paclitaxel. Improvement in the median duration of response occurred in the entire cohort who received trastuzumab overall. This was also
true in both subgroups.

| Table 1. — Phase III Clinical Trial Comparing Best Available Chemotherapy to Same Therapy Plus Trastuzumab |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Enrolled | Response Rate (%) | Response Duration (mos) | Time to Progression (mos) |
| T + CT | 235 | 49 (53% increase) | 9.3 (58% increase) | 7.6 (65% increase) |
| CT | 234 | 32 | 5.9 | 4.6 |
| T + AC | 138 | 12 (20% increase) | 2.1 (40% increase) | 1.8 (33% increase) |
| AC | 145 | 42 | 5.5 | 6.1 |
| T + P | 92 | 82 (163% increase) | 11.0 (150% increase) | 6.9 (130% increase) |
| P | 96 | 16 | 4.4 | 3.0 |

Trastuzumab was found to have a significant impact on time to disease progression — the primary endpoint. The survival data showed
that one year after treatment patients were alive vs 78% of patients who had received chemotherapy plus
trastuzumab. Updated to April 1999, 36% of patients were alive with chemotherapy alone vs almost 50% when chemotherapy was
combined with trastuzumab. These results were achieved in spite of the fact that women who were randomized to the chemotherapy-
alone arm at the time of progression were permitted to subsequently receive trastuzumab. Of the 65% who elected this option, one third
responded. The median survival of the population who received trastuzumab plus chemotherapy was lengthened by a factor of almost
25%.

Clinical Safety: Cardiac Toxicity

Trastuzumab was found to be generally well tolerated, both as a single agent and in combination with chemotherapy. Most adverse
events (eg, mild fevers and chills) were mild to moderate and could be controlled with acetaminophen or diphenhydramine hydrochloride.
These symptoms generally occurred with the initial infusion but not with subsequent infusions. However, the incidence of cardiac
dysfunction significantly increased when trastuzumab was used concomitantly with anthracycline or used by women who had received
prior anthracycline (Table 2). Using the New York Heart Association cardiac dysfunction events scale, we found a more than fourfold
increase in cardiac dysfunction when trastuzumab was used simultaneously with anthracycline (38%) than with anthracycline alone
(9%). This trend carried over to the paclitaxel subgroup, in which 2% of patients experienced cardiac dysfunction with paclitaxel alone vs
11% (adjusted to 12% after FDA review of the data) with paclitaxel given concomitantly with trastuzumab.

| Table 2. — Trastuzumab in Combination With Chemotherapy: Cardiac Dysfunction Outcomes |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| T + AC | 39 | AC | 9 | T + P | 11 |
| P | 2 |
| Herceptin Therapy Post Events (%) | 14 | 5 | 6 | 1 |

| Deaths (%): |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Metastatic Breast Cancer | 4 | 0 | 8 | 2 |
| Cardiac | 0 | 1 | 0 | 0 |
| Pneumonia | 0 | 0 | 1 | 0 |

Overall, trastuzumab is an effective drug for HER2/neu-positive metastatic breast cancer patients. Future trials with trastuzumab not only
will shed light on which patients will receive the most benefit, but also will investigate its use as an adjuvant treatment for localized breast
cancer. It will also be studied with other chemotherapeutic drugs (eg, cisplatin or carboplatin) and in other tumors.

Conclusions

The addition of trastuzumab to chemotherapy significantly increases clinical benefit for patients with metastatic breast cancer with
confirmed HER2 overexpression. There is no increase in severe adverse events other than a significant increase in cardiac dysfunction in
patients concurrently using anthracycline and in patients who had received prior anthracycline.
References

Discussion

Dr Horton: Can you summarize your thinking about the most effective tests for HER2 that clinicians should order?

Dr Slamon: There are four basic assays available now: (1) solid matrix blotting techniques, (2) serum-based assays, (3) immunohistochemistry, and (4) fluorescence in situ hybridization (FISH). The traditional solid matrix blotting techniques require obtaining pieces of tumor and extracting macromolecules — DNA, RNA or proteins — and testing them. I don’t think this is efficient enough to achieve wide acceptance. The very sensitive serum-based assays would be the easiest to use to test for this alteration, by measuring the extracellular domain of the receptor that is shed, but these are less useful to follow early disease or minimal disease and as screening tools. Immunohistochemistry is the most commonly used assay. It’s generally available, all laboratories know how to do it, and there is a wide variety of antibody reagents. Gene-based imaging using FISH is a new technique that appears to be superior to immunohistochemistry. For example, even when using the best available antibodies that have the best sensitivity, there will still be a 20% miss rate with immunohistochemistry. The downside is that FISH is not generally available; it’s a new technique that requires special instrumentation. Another drawback is that it will miss the single-copy overexpressers. The immunohistochemical kit HercepTest (DAKO Corp, Carpinteria, Calif) introduced antigen retrieval in which the specimen is “cooked” in either a microwave or a water bath to enhance the staining. However, except in central laboratories where there is substantial experience with this, the results have been disastrous. Positivity rates are coming in at 50%, 60%, and sometimes 70%.

Dr Horton: What are your recommendations about either stopping or continuing trastuzumab in a patient whose disease progresses on trastuzumab plus chemotherapy and you stop the chemotherapy?

Dr Slamon: Most people are thinking that since the drug is so well tolerated when it is not used with anthracycline that you can continue the drug and then add other chemotherapy. You may see some of the additive effects that we’ve seen. In the case of the platinum salts, we’ve had patients who had failed and then had complete responses to either cisplatin or carboplatin. So my recommendation is to continue the drug unless there is a problem with toxicity.

Dr Horton: A related question: how long should one continue trastuzumab in a patient who is doing well?

Dr Slamon: There is no answer. We have patients on both ends of the spectrum. The longest surviving patient on trastuzumab had metastatic disease in the lungs and bulky nodal disease. She has been disease-free for seven years and is on no active therapy after receiving 18 weeks of the drug. Similarly, we had a patient with significant liver disease (about 60% of her liver was involved) who had a complete response. She refused to go off the drug and has been on it continuously for five years, weekly, with no untoward effects. Of course, that’s been done in a study setting. We do not know how practical that will be, economically, in the actual setting. The short answer to your direct question is we don’t know how long to use this drug. The adjuvant trial designs are going on at six and 12 months of therapy and then stopping. I think, biologically, that range will probably be in the six- to nine-month range.

Dr Horton: How often do you consider directly monitoring cardiac function in patients who are taking trastuzumab for an appreciably long period of time?

Dr Slamon: In the trial designs, we have recommended monitoring at baseline and then every 12 weeks thereafter. The interesting thing that came out of the clinical trial is that we got a lot of warning. We were not watching cardiac function closely because we didn’t expect this side effect. However, once we saw it, we immediately, carefully, studied the women on the trastuzumab-alone group. So, the recommendation is if you are going to use it in patients who have had prior anthracycline or are close in time to anthracycline therapy, monitor them every 12 weeks.
Dr Horton: What's your sense about the future of trastuzumab in patients whose tumors test negative by whatever test is used?

Dr Slamon: There are now early clinical data indicating that those patients aren’t responding better to trastuzumab than to chemotherapy alone. It has been tried with paclitaxel for non-HER2 overexpressers. I think that if we had seen a lot of activity in non-overexpressing tumors, we would have expected to see the toxicity profile of the drug to be much higher because the levels of the receptor expressed in non-altered breast cancers are essentially identical to that seen in normal epithelial tissues — lung, kidney, liver, GI tract. And we did not see significant increases in toxicity in those patients when the drug was used.

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