Trastuzumab: Further Considerations

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One of the best examples of the “bench to bedside” process is the development of trastuzumab (Herceptin) for HER2-overexpressed breast tumors. From the identification of the neu oncogene in 1984[1] and its subsequent cloning,[2] to the development of a humanized monoclonal antibody targeting HER2 that improved outcome not only in the metastatic setting[3] but also in the adjuvant setting[4-7] has been a long yet fruitful journey.

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Trastuzumab: When, for How Long, and for Whom?
Results from five randomized adjuvant trials—the Herceptin Adjuvant (HERA) trial, the combined North American National Surgical Adjuvant Breast and Bowel Project (NSABP)31 and North Central Cancer Treatment Group (NCCTG) N9831 trials, the Breast Cancer International Research Group (BCIRG) 006 trial, and the Finnish trial—have established the efficacy of trastuzumab in women with early-stage HER2-positive breast cancer. Despite short follow-up, consistent results of reduction in odds of recurrence and mortality were seen across all five trials. Although the results are remarkable, the varying designs of all five trials have resulted in a number of questions. The North American[5-7] and HERA[4] trials used 1 year of adjuvant trastuzumab, whereas the Finnish trial used only 9 weeks of trastuzumab to achieve similar efficacy results. As the number of patients enrolled in the Finnish study was small, the result is not likely to change clinical practice; but it is food for thought. A shorter but equally efficacious trastuzumab regimen may reduce the incidence of associated cardiac morbidity, decrease the risk of developing resistance to the antibody, and would be more cost friendly.

Defining a group of patients that would receive maximum benefit from trastuzumab is difficult because of the heterogeneous nature of breast tumors. Kim et al[8] showed that coamplification of cMyc and HER2 predicted for a superior recurrence-free survival by balancing the proapoptotic function of dysregulated cMyc with the antiapoptotic signal induced by trastuzumab. However, patients with HER2 tumors that do not have amplification of cMyc still derive a benefit, although smaller, from trastuzumab. As yet there is no way to identify a subset of patients with HER2-positive disease that would not benefit from trastuzumab. The question of optimal timing of trastuzumab has also been an area of extensive research. The average delay in trastuzumab administration after surgery was 8 months in the HERA trial,[4] 4 months in the NSABP-31/N9831 trials,[5] and 1 month in the Finnish trial.[6] The control group in the HERA trial[9] showed that the maximum risk of relapse occurred in patients with more than four positive lymph nodes (irrespective of hormone receptor status) and in patients with hormone receptor-negative disease. The superior disease-free survival seen in the NSABP-31/N9831 trials as compared to the HERA trial suggests that concomitant administration of trastuzumab with chemotherapy may be a better approach. Both pieces of information may persuade clinicians to start trastuzumab treatment early rather than later with concomitant administration of chemotherapy at least in the high-risk cohort of patients.

Cardiac Toxicity: Are We Being Too Cautious?
Although generally safe, trastuzumab is known to be associated with cardiac toxicity. This was observed early on in studies with patients who had metastatic disease, especially those who had been treated with concomitant anthracycline and trastuzumab.[15] This led to subsequent adjuvant
trials avoiding the concomitant use of trastuzumab and an anthracycline. Proposed mechanisms of trastuzumab cardiac toxicity include the induction of immune-mediated destruction of cardiomyocytes, the requirement of HER2 signaling for myocyte survival and drug-drug interactions.[16-18]

With the use of stringent cardiac evaluation guidelines, the HERA trial[4] observed a rate of 1.73% of New York Heart Association class III or IV congestive heart failure (CHF), while that observed in the NSABP-31 trial[19] was 4.1%. The lower rate of severe CHF observed in the HERA trial may reflect the longer time allowed for the myocardium to recover from anthracyclines before the initiation of trastuzumab. Conversely, the higher rate observed in the NSABP-31 trial could be explained by the concomitant use of taxanes, which may have enhanced the trastuzumab-induced cardiac toxicity. Despite increased cardiotoxicity when trastuzumab is combined with an anthracycline, we cannot ignore the fact that the combination of the two has significant activity. Interestingly, Buzdar and colleagues[20,21] showed that the sequential use of four cycles of paclitaxel followed by four cycles of FEC (fluorouracil, epirubicin [Ellence], cyclophosphamide), all administered with concurrent trastuzumab (for 24 weeks), was safe, with only 10% of patients developing grade 1 or 2 cardiac toxicity and 65% of patients achieving a complete pathologic response. Preliminary evidence also shows that the combination of trastuzumab with liposomal doxorubicin (Doxil) may be safe and effective.[22] In addition, the Finnish study that used only 9 weeks of trastuzumab after anthracycline therapy showed no evidence of cardiotoxicity at a median follow-up of 3 years, indicating that the cardiotoxicity rate observed in the HERA and North American trials were probably due to the longer (1-year) duration of trastuzumab administration. These data beg the question of whether we are being too cautious in not combining trastuzumab with an anthracycline. We should be examining strategies such as combining trastuzumab with less-cardiotoxic anthracyclines and using shorter trastuzumab regimens. However, we will have to wait until the safety of these approaches is tested in large prospective randomized trials.

HER2 Testing: Guidelines Are Important

Amplification of the HER2 gene, resulting in the overexpression of HER2 protein on the surface of cells, occurs in 25% to 30% of all breast tumors.[23] Trastuzumab specifically targets the HER2 receptor, with strongly HER2-positive tumors obtaining the most clinical benefit. Accurate testing of HER2 is therefore important, having implications for not only correctly identifying patients who would benefit from trastuzumab, but also identifying those who would not and thus preventing unnecessary exposure to an agent that is not without side effects.

The optimal testing strategy for HER2 has long been an issue of debate and controversy. The two most commonly used methods of testing include immunohistochemistry (IHC) testing for the HER2 surface protein and fluorescence in situ hybridization (FISH), which is a semiquantitative method to directly detect HER2 gene amplification. One of the biggest problems encountered is a poor concordance between HER2 test results from local laboratories and those from large-volume reference laboratories using either IHC or FISH methods.[24] Small-volume laboratories, performing on average less than 100 assays per month, have shown the biggest discordance in HER2 results.[24,25] Recent results from the N9831 trial[26] confirmed these findings showing that a considerable proportion of patients found to be strongly positive for HER2 in local laboratories were not subsequently confirmed as such when tested at a central laboratory (18.4% for IHC and 11.9% for FISH). In addition, the trial also showed a > 95% concordance between results of testing done at a central laboratory and that done at a reference laboratory (ie, a high-throughput commercial facility). Recognizing a need to address this issue, a National Comprehensive Cancer Network task force[27] convened to make recommendations about the interpretation of test results. Similar guidelines were also published in the United Kingdom.[28]

Understanding Resistance

Resistance to trastuzumab is not uncommon, as evidenced by the fact that no more than one-third of patients respond to initial trastuzumab monotherapy in the metastatic setting. Moreover, in the adjuvant setting, trastuzumab reduces the annual hazard rate by half (ie, half the recurrences are not prevented). The inability of trastuzumab to cross the blood-brain barrier is one mechanism of resistance that may explain the development of central nervous system metastases in patients with responding peripheral metastases.[10] Other potential mechanisms of resistance include loss of HER2 amplification, inactivation of PTEN,[11] masking of HER2 (and thus inhibition of trastuzumab binding) by membrane-associated mucin MUC4,[12] truncated HER2 receptor (p95\text{Erbb2}),[13] and downregulation of the cyclin-dependent kinase p27\text{kip1}.[14]
recent 15-year update of the meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed that 6 months of adjuvant anthracycline-based combination therapy reduces the annual breast cancer death rate by 38% in women younger than 50 years and by 20% in women aged 50 to 69 years.[22] The results of the recent adjuvant trastuzumab trials show further decreases in the risk of disease recurrence and death in patients with HER2-positive disease. In order to improve these results further, we need to accurately select patients with HER2-positive disease, identify cohorts of patients who would receive maximum benefit from trastuzumab, and identify ideal trastuzumab/chemotherapy combinations that have maximum efficacy with minimal toxicity. Furthermore, understanding the mechanism of resistance to trastuzumab would open avenues to new drug development. Finally, cost cannot be ignored, and it would be prudent to allocate resources toward dealing with this issue, to make drugs like trastuzumab available to everyone, everywhere.

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