Trastuzumab: Is the new evidence revolutionary?

ABSTRACT
A few years back, the survival benefit of trastuzumab in HER2 positive breast cancer patients presenting with metastatic disease was proven in a randomized setting. Recently a number of randomized trials have reported their results in the adjuvant setting in HER2 positive patients. These trials have been considered by some as a landmark in the evolution of breast cancer management. Although the data is encouraging, it need to be seen in a proper perspective keeping in mind the limitations and the side effects reported. This article stresses the use of Herceptin in carcinoma breast patients in adjuvant setting with a cautionary eye.

KEY WORDS: Trastuzumab, evidence, revolutionary

There has been a tremendous interest recently in the literature and media about the emergence of trastuzumab as a significant and vital component in the adjuvant management of patients with breast cancer with HER2 overexpression. This has been even acclaimed as a revolutionary emergence and hailed as a very significant advance. While there is little doubt that the recent data is most encouraging, the question obviously is that, is it compelling enough to pass such judgment? Several questions, including short follow-up; difference in survival between the studies; long-term effects on cardiac and other toxicities, particularly as combined with taxanes and concomitant radiation therapy, do somewhat tamper the unbridled enthusiasm displayed by lay and medical literature alike. The implications in our country need to be examined as well, particularly with respect to feasibility.

Patients with breast cancer and HER2 amplification or overexpression are likely to have associated poor prognostic features such as poorly differentiated tumors, positive axillary lymph nodes and decreased expression of ER and PR receptors. All these characteristics are associated with an increased risk of disease recurrence and death. Trastuzumab is a monoclonal antibody targeting the extracellular domain of the HER2 protein. It is a rare example of a success story of clinical and translational medicine moving from bedside to bench to bedside. The agent was approved in 1998 as a first-line treatment in combination with paclitaxel for HER2-positive metastatic breast cancer and subsequently a phase III randomized trial showed a survival benefit with trastuzumab in metastatic breast disease. Following this, the National Cancer Institute (NCI) sponsored two trials of adjuvant treatment with trastuzumab, led by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the North Central Cancer Treatment Group (NCCTG) and the results of these were published in NEJM in 2005. Another trial, known as the adjuvant trastuzumab (HERA) trial, was also reported simultaneously.

While the NSABP and the NCCTG administered paclitaxel concurrently with trastuzumab, the HERA trial gave sequential trastuzumab after completion of paclitaxel chemotherapy. Do the findings of these trials herald a paradigm shift in adjuvant systemic therapy for HER2-positive breast cancer patients?

Benefit from trastuzumab
An interim analysis done for the NSABP-31 found such a startling difference between the trastuzumab and control arms that further accrual was stopped in the trial. There were 133 events (recurrence of breast cancer, metastasis contralateral breast cancer, second non-breast malignant disease or death) in the trastuzumab group and 261 in the control group (hazard ratio, 0.48; \( P < 0.0001 \)). The absolute difference in disease-free survival between the trastuzumab group and the control group was 12% at 3 years. Trastuzumab therapy was associated with a 33% reduction in the risk of death (\( P = 0.015 \)). Indeed, the impressive results led some clinicians to believe that this signified not an evolution but a revolution for breast cancer management. In the HERA study, at median follow-up of 1 year, 347 events were observed: 127 events in the trastuzumab group and 220 in the observation group, a finding similar to that of NSABP-31 (hazard ratio, 0.54; \( P < 0.0001 \)). The interesting difference however was that survival was not different in different arms of the HERA trial, which is very pertinent as it could probably indicate...
the ineffectiveness of trastuzumab in adjuvant setting when used sequentially as compared to concurrently with paclitaxel. Till the data matures significantly, real answers will remain a mirage.

There are other important differences between the two reports that need to be emphasized. In spite of the fact that one-third of patients included in the HERA trial had negative lymph nodes (which would indicate a better overall prognosis for this patient population), the disease-free survival curves of both the control group and the trastuzumab group of the combined North American report fared better than the corresponding groups in the HERA trial. One hypothesis for explaining this would be the fact that only 26% of the patients in the HERA trial received a taxane, whereas all patients in the combined analysis received paclitaxel.

What is the optimal duration of giving trastuzumab? Trastuzumab was given for 1 year in the NSABP-31 and the NCCTG trial N9831. In the HERA trial, one group of women received trastuzumab for 1 year and another group received the drug for 2 years. The authors provided three reasons for prolonged therapy arm: 1) A major peak in the rate of relapse in breast cancer occurs 18 to 24 months after surgery. \[6\] 2) Effective treatment of HER2-positive breast cancer may require prolonged attenuation of HER2 activity. \[7\] 3) Tamoxifen, which is another effective targeted therapy for breast cancer, is most beneficial when given for longer than 1 year. \[8\] The issue of optimal duration of trastuzumab is therefore begging for an answer.

Other unanswered questions include the safety of giving radiotherapy concurrently with trastuzumab.

Morbidity of trastuzumab

The major adverse events associated with trastuzumab are hypersensitivity and cardio toxicity (principally congestive heart failure). Cardio toxicity has been reported in 1.4% of women who received this drug as a single agent for metastatic disease. \[9\] However, by the regime as suggested and administered by the NSABP-31 and the NCCTG trial N9831, the heart is insulted 1) by Adriamycin in AC regime 2) by use of paclitaxel and trastuzumab 3) by concurrent use of radiotherapy with paclitaxel and trastuzumab. It has already been reported by the Early Breast Cancer Trialists’ Collaborative Group that patients treated by radiotherapy for breast cancer show an increased mortality rate from cardiovascular events. In a meta-analysis involving 19,582 patients, they reported that RT reduced the annual mortality from breast cancer by 13% but increased the annual mortality rate from other causes by 21% and that this increase was due primarily to an excess number of deaths from cardiovascular causes. \[10\] Similar findings have been suggested by meta-analysis reported by Cuzick et al involving 7,941 women, in which it was found that standardized mortality ratio in breast cancer patients was greater for patients treated with RT compared to controls. \[11\] Using radiotherapy concurrently with trastuzumab can make an ingredient of a lethal cocktail.

Even with the stringent criteria observed in the above trials, there were six fatal adverse events in the trastuzumab group and three in the observation group in the HERA study. The scenario was worse for the NSABP-31, in which the cumulative incidence of New York Heart Association class III or IV congestive heart failure or death from cardiac causes at 3 years was 0.8% in the control group (4 patients had congestive heart failure and 1 died from cardiac causes) and 4.1% in the trastuzumab group (31 patients had congestive heart failure). In the earlier reported randomized trial for trastuzumab in metastatic disease, 15 patients in the subgroup given an anthracycline, cyclophosphamide and trastuzumab; and 3 in the subgroup given paclitaxel and trastuzumab had clinical signs of cardiac dysfunction. \[12\]

What is still unknown is the exact nature of cardiac dysfunction, its potential reversibility, the long-term effects of even treatable congestive heart failure and the kind of intervention that will be required in most such cases.

Follow-up duration in trastuzumab trials

Breast cancer has a definite pattern of events, as has been suggested by the latest EBCTCG study. \[12\] While three-fourths of the loco-regional events occur by 4-5 years of diagnosis, survival differences start to appear after 3-4 years and then achieve prominence by 10-15 years. The median duration of follow-up has been 2.4 years and 1.5 years in NSABP-31 and the N9831 trial respectively, while HERA has a median follow-up of 1.5 years. It is therefore not prudent to comment on the overall survival rates at this stage. Furthermore, it also takes more than 15-year median follow-up since the cardiac effects take such a long time to manifest completely. \[12\] While the cardiac morbidity is within apparently reasonable limits at this stage in the trials, the true picture will emerge only after 15 years.

Cost of trastuzumab

It is important to keep the cost factor in mind while planning trastuzumab as a component of systemic adjuvant therapy in breast cancer, even in the West. The entire course of treatment in our country costs between Rs. 16 and 18 lakhs (1.6 and 1.8 million), which is clearly a huge amount by any standards with the setup prevailing in our country. While this amount can be taken care of by insurance companies in the West, the health care system is ill-equipped in India to support such treatment for the public at large. To add to this is the rather odd schedule of weekly chemotherapy.

To summarize, although trastuzumab has shown positive results and raised hopes in treatment of HER2-positive breast cancer, we need to be cautious in interpreting the results at this stage. Time itself will yield the final answers for survival and toxicity results in these trials. Future trials could consider a randomized comparison between concurrent and sequential
trastuzumab on one hand and concurrent versus sequential radiotherapy with trastuzumab on the other. The final word on trastuzumab in adjuvant treatment of HER2-positive breast cancer is yet to be written.

REFERENCES


Source of Support: Nil. Conflict of Interest: None declared.