Herceptin in early breast cancer: A call for judicious use

Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang C-S, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Süt T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD, for the Herceptin Adjuvant (HERA) Trial Study Team. (Department of Medicine, Breast International Group Secretariat and Breast European Adjuvant Study Team Data Centre; Jules Bordet Institute, Université Libre de Bruxelles, Brussels; Frontier Science [Scotland], Kingussie, Scotland; Department of Oncology, Gerald Bronfman Centre for Clinical Research in Oncology, McGill University, Montreal; Department of Medicine, European Institute of Oncology, Milan, and the Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; Klinik für Frauenheilkunde und Geburtshilfe, Ludwig-Maximilians-Universität München, Grosshadern, Munich, Germany; Breast Unit, Royal Marsden Hospital and Institute of Cancer Research, London; Struttura Complessa Oncologia Medica 1, Istituto Nazionale per lo Studie e la Cura dei Tumori, Milan; Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona; Andrew Love Cancer Centre, Geelong Hospital, Geelong, Australia; Department of Gynecology, Philipps University of Marburg, Marburg, Germany; Department of Oncology, Western General Hospital, Edinburgh; Department of Academic Biochemistry, Royal Marsden National Health Service Trust, London; Hospital São Lucas, Pontifícia Universidad Catòlica do Rio Grande do Sul School of Medicine, Porto Alegre, Brazil; Department of Internal Medicine, Medical University of Vienna, Vienna; Department of Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei; Department of Oncology, Finsen Center, Rigshospitalet University Hospital, Copenhagen; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; N.N. Blokhin Cancer Research Center, Moscow; Department of Oncology, National Institute of Oncology, Budapest, Hungary; Frauenklinik der Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany; Department of Breast Oncology, Aichi Cancer Center, Aichi, Japan; Klinik und Poliklinik für Gynäkologie, Universitätsklinikum Hamburg Eppendorf, Hamburg, Germany; Department of Medical Oncology, British Columbia Cancer Agency, Vancouver Centre, Vancouver, B.C., Canada; Swiss Cardiovascular Center, Bern, Switzerland; Institut für Pathologie, Klinikum Kassel, Kassel, Germany; F. Hoffmann-La Roche, Basel, Switzerland; and Department of Biostatistics and Computational Biology, Dana–Farber Cancer Institute, Boston.) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;**353:** 1659–72.

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SUMMARY

HERA trial

In this trial, women were randomly assigned to one of three arms—2 years of treatment with trastuzumab (1694 women), 1 year of treatment with trastuzumab (1694 women) and observation (1693 women). The investigators reported the results only of treatment with trastuzumab for 1 year and observation.

Patients treated for 1 year with trastuzumab received the first dose of 8 mg/kg followed by 6 mg/kg every 3 weeks for 1 year. Eight per cent of patients discontinued the treatment either due to worsening of cardiac function (5.5%) or by their choice, and 26% received taxanes in addition to anthracycline-based chemotherapy.

At the first planned interim analysis (median follow up of 1 year), the unadjusted hazard ratio (HR) for an event in the trastuzumab group as compared with the observation group was 0.54 (95% CI: 0.43–0.67; $p<0.0001$), representing an absolute benefit of 8.4% in terms of disease-free survival (DFS) at 2 years. Distant recurrence-free survival was also better in the trastuzumab arm (HR: 0.49; 95% CI: 0.38–0.63; $p<0.0001$). Overall survival in the two groups was not significantly different (HR: 0.76). Severe cardiotoxicity developed in 0.5% of women treated with trastuzumab.

This means that the use of trastuzumab in the adjuvant setting for 1 year reduces recurrence by 46% and distant recurrence by 51%. A 24% reduction in the risk of death reached statistical significance within this short duration of follow up.

NSABP B31 and N9831 trials

*NSABP B31.*The National Surgical Adjuvant Breast and Bowel Project trial B31 compared doxorubicin and cyclophosphamide followed by paclitaxel every 3 weeks (group 1) with the same regimen along with 52 weeks of trastuzumab beginning with the first dose of paclitaxel (group 2). Groups 1 and 2 had 872 and 864 patients with follow up, respectively.

*N9831.*The North Central Cancer Treatment Group trial N9831 compared three regimens: doxorubicin and cyclophosphamide followed by weekly paclitaxel (group A), the same regimen followed by 52 weeks of trastuzumab after paclitaxel (group B), and the same regimen along with 52 weeks of trastuzumab initiated concomitantly with paclitaxel (group C). Groups A and C had 807 and 808 patients with follow up, respectively.

The studies were amended to include a joint analysis comparing groups 1 and A (the control group) with groups 2 and C (the trastuzumab group). Group B was excluded because trastuzumab was not given concurrently with paclitaxel. Patients in the trastuzumab arms received the first dose of 4 mg/kg followed by 2 mg/kg every week for 1 year. About one-quarter of patients (24.9%) discontinued the treatment either due to worsening of cardiac function (18.9%) or by their choice.

The HR for an event in the trastuzumab group was 0.48 (p<0.0001). The absolute difference in DFS between the trastuzumab group and the control group was 12% at 3 years. Distant recurrence-free survival was also better in the trastuzumab arm (HR: 0.47; p<0.0001). Trastuzumab therapy was associated with a 33% reduction in the risk of death (HR: 0.67; p=0.015). The three-year cumulative incidence of class III or IV congestive heart failure or death from cardiac causes in the trastuzumab group was 4.1% in trial B31 and 2.9% in trial N9831.

This means that concurrent trastuzumab with paclitaxel in the adjuvant setting for 1 year reduces recurrence by 52% and distant recurrence by 53%. There is also a 33% reduction in the risk of death.

COMMENT

The third week of October 2005 saw a remarkable triumph of translational research. Simultaneous publication of these trials of adjuvant trastuzumab (herceptin) declared it a new 'standard-of-care' in the management of breast cancer. These results increase our faith in basic and translational research. However, while we celebrate this achievement of 'bench-to-bedside medicine', we need to be careful of the possibility of a wave of aggressive marketing, leading to indiscriminate use of the drug. This may do more harm than good. The current evidence calls for careful case selection and judicious use.

What is herceptin?

Trastuzumab is a monoclonal antibody against the HER-2 receptor (human epidermal growth factor receptor) produced in only 15%–20% of breast cancers.[1] HER-2 positive breast cancers have a worse prognosis than HER-2 negative ones. This drug is effective only in HER-2 positive breast cancers.

The *HER-2/neu* gene is a member of a family of genes encoding transmembrane receptors for growth factors. The intracellular domain of HER-2 has tyrosine kinase activity that regulates important aspects of the physiology, growth and differentiation of cells.

Testing for HER[2]

Fluorescence *in situ* hybridization (FISH) detection of provides the most accurate information about expression of the *HER-2* gene. Immunohistochemistry (IHC), though widely available, has many drawbacks such as variations in fixation methods, techniques and interobserver variability. Also, detection of *HER-2* positivity by FISH correlates better with response to therapy and survival than detection by IHC. Since FISH is not yet widely available, screening for the HER-2 protein by IHC, backed by rigorous quality controls and FISH testing of equivocal cases with intermediate staining intensity (score 2; score 1 indicates negative *HER-2* status and score 3 indicates positive *HER-2* status) appears to be the most feasible practical option.

What is the importance of the results of these trials?

After a long time, a cancer drug has offered such a remarkable improvement in survival. Herceptin reduces the risk of recurrence of cancer by almost 50%. Though these early results show a 24%–33% relative improvement in overall survival, a 50% reduction in distant recurrence (which usually kills the patient) strongly supports the possibility of similar reductions in the risk of death.

The importance of this survival benefit is better assessed by a comparison with other therapeutic options (Table I). Anthracycline-based polychemotherapy[4] improves survival (relative improvement) by 38% in premenopausal and by 20% in postmenopausal women. Tamoxifen improves survival by 31% in breast cancers expressing oestrogen receptor (ER).[4] Docetaxel, doxorubicin, cyclophosphamide (TAC)[5] show 30% improvement in survival as compared to fluorouracil, doxorubicin, cyclophosphamide (FAC). If the benefit of TAC is extrapolated to calculate its efficacy over no chemotherapy, the improvement in survival will reach 50%.

What are the concerns of such therapy?

The most worrying adverse effect of this drug is its cardiotoxicity. Cardiotoxicity is greater when patients have received anthracyclines and when trastuzumab is used concurrently with chemotherapy. The NSABP B31 trial[5] reported a 4.1% incidence of severe cardiotoxicity, and almost 19% of patients discontinued trastuzumab due to cardiac dysfunction.

In a hypothetical patient with a possible absolute improvement in survival of 4%, the entire benefit can get nullified by the 4%

TABLE I. Comparison of survival benefit with different adjuvant chemotherapy regimens for breast cancer

Intervention	*n*	Follow up (years)	Relative risk (survival)		Cardiac morbidity (%)
			Disease-free	Overall	
Herceptin sequential (HERA trial)*†	3387	1	0.54	0.76	1.7
Herceptin sequential (HERA trial)‡	873	1	0.77	–	
Herceptin concurrent with taxanes (NSABP31 and N9831 trials)§	3351	1	0.48	0.67	4.1 (NSABP31)
TAC *v*. FAC[3]	1491	4.5	0.72	0.70 ‖	1.6
Anthracyclines *v*. none (<50 years)[4]	8000	15	0.67	0.62 ‖	0.08 per year
Anthracyclines *v*. none (>50 years)[4]			0.79	0.80	
CMF *v*. none (<50 years)[4]	14 000	15	0.59	0.66	0.06 per year
CMF *v*. none (>50 years)[4]			0.81	0.90	

* anthracycline or anthracycline and taxanes-based chemotherapy † 2-year survival rates
‡ anthracycline and taxane-based chemotherapy § 3-year survival rates ‖ current standards of care
TAC docetaxel, doxorubicin and cyclophosphamide FAC fluorouracil, doxorubicin and cyclophosphamide
CMF fluorouracil, methotrexate and cyclophosphamide
Note: A relative risk of 0.70 in disease-free survival means a 30% relative reduction in the chance of recurrence.

chance of cardiotoxicity. Since it is impossible to predict with certainty whether a particular patient will benefit from the drug or not, and whether that patient will have cardiac side-effects or not, one has to depend on statistical probabilities.

Where does herceptin fit in with the current adjuvant therapy scene?

One important difference in these trials is that only 26% of patients in the HERA trial received taxanes. This probably reflects in the overall results, where the control group in the HERA trial fares much worse compared with the control group in the other two trials (2-year DFS 77.4% *v*. 83%; based on calculations from the survival graph). The reduction in recurrence is 23% in the taxane subgroup in the HERA trial.

Additionally, the cardiotoxicity was much lower (1.7%) in the HERA trial (sequential trastuzumab). This may mean that cardiotoxicity is lower when trastuzumab is not used concurrently with the taxanes, but the benefits of therapy are also reduced.

Current evidence favours the use of taxanes in adjuvant settings, especially TAC[5] in patients with a good performance status. However, since adjuvant TAC itself has higher cardiac and other toxicities, concurrent use of trastuzumab may prove risky. Hence, in all probability, herceptin sequential to TAC would seem to be the best treatment option; but only in patients with good performance status.

The economics

It is difficult to specify the cost of different chemotherapy regimens available in India due to a wide range of generic drugs and original research products. An anthracycline-based chemotherapy regimen costs about Rs 20 000–30 000, a docetaxel-based chemotherapy regimen (TAC) costs about Rs 200 000–300 000 and 5 years of tamoxifen therapy costs Rs 4000–5000. However, 1 year of herceptin therapy will cost about Rs 2 000 000. All patients who can afford herceptin will be able to afford any other form of systemic therapy.

Should all HER-2 positive patients be given herceptin?

Certainly not. This is where careful selection based on value judgement is of paramount importance. The anticipated benefits of trastuzumab in a particular patient will have to outweigh its possible hazards before it can be recommended to that patient. I provide 2 examples of such possible scenarios:

Example 1: A premenopausal patient with a 4 cm ER-negative tumour with 4 of 16 lymph nodes showing metastasis has a 35%–40% chance of recurrence. She will still have a 17%–20% chance of recurrence after administration of the best adjuvant chemotherapy. Her survival can be improved by almost 10% by administering trastuzumab and the net benefit after accounting for cardiotoxicity will still be more than 5%. Such a patient will be a well-deserving candidate for trastuzumab.

Example 2: A 60-year-old lady with a 3 cm ER-positive tumour without nodal metastasis has a 10%–12% chance of recurrence. Her chances of recurrence will be reduced to 4%–5% after the use of anthracycline-based chemotherapy and hormone therapy. In such a patient trastuzumab will have a very modest benefit of 2%–3%, not enough to recommend it to her in view of the adverse effects.

Oncologists will have to assess the possible benefits and harms for each patient before recommending such therapy. They need to remember that only patients with good performance status and cardiac function should receive this drug.

Unanswered questions

Duration of therapy. One year or 2 years and concurrent use or sequential use are the questions that will probably be answered once results from the other arms of these trials are published.

How much improvement occurs in overall survival and what the long term consequences of the cardiotoxicity are will probably be known when longer follow up results are published.

Weekly administration or a 3-weekly schedule for trastuzumab is a question that remains unanswered and a decision on this will be based on the logistics of administration till the question is conclusively answered, maybe in a new randomized trial.

Recently, adjuvant TAC has emerged as a new standard-of-care. This regimen itself has a higher cardiotoxicity and other adverse effects, but also shows significant improvement in survival. How should one administer trastuzumab in a patient on adjuvant TAC? Will it result in very high cardiotoxicity? These are the questions only new trials and time can answer.

To conclude, herceptin is a promising new drug on the horizon of breast cancer adjuvant treatment. It can only be used in patients with HER-2 positive breast cancers and only after careful case selection in view of the side-effects.

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MANGESH A. THORAT
Department of Surgical Oncology
Tata Memorial Hospital
Dr E. Borges Marg
Parel
Mumbai
Maharashtra
thoratmangesh@gmail.com