

CAN WE CURE BREAST CANCER WITH ADJUVANT TRASTUZUMAB?

Evaluating the costs and benefits

Joseph Ragaz, MD, FRCPC

Top-line summary

The news of the results from 3 recent trials of adjuvant trastuzumab treatment in early breast cancer, showing a large reduction in cancer recurrence in women with HER2-positive (HER2+) disease, is a major success for the concept of targeted therapy using biological agents. Because 20% to 30% of all newly diagnosed women have HER2+ breast cancer, making trastuzumab available to all those who stand to benefit entails huge costs for healthcare providers — an estimated \$C160 million per year in Canada. Here, Joseph Ragaz, MD, a member of the Editorial Advisory Board of *Oncology Exchange*, reports the key findings of the 3 trials, NSABP B-31, NCCTG-N9831 and HERA, as presented at the recent Annual Meeting of the American Society of Clinical Oncology (ASCO), and proposes an approach for how decision-makers should evaluate the costs and benefits of this treatment.

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Very few developments have galvanized the breast cancer establishment more profoundly than the April 25, 2005 news alert from the US-based National Institutes of Health (NIH). An unexpectedly large benefit was reported for trastuzumab given as adjuvant treatment to women with HER2+ early breast cancer in 2 trials conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the North Central Cancer Treatment Group (NCCTG).

Both study groups halted patient accrual and recommended that all women enrolled in the observation arms be offered treatment with trastuzumab.

TRIAL OUTCOMES

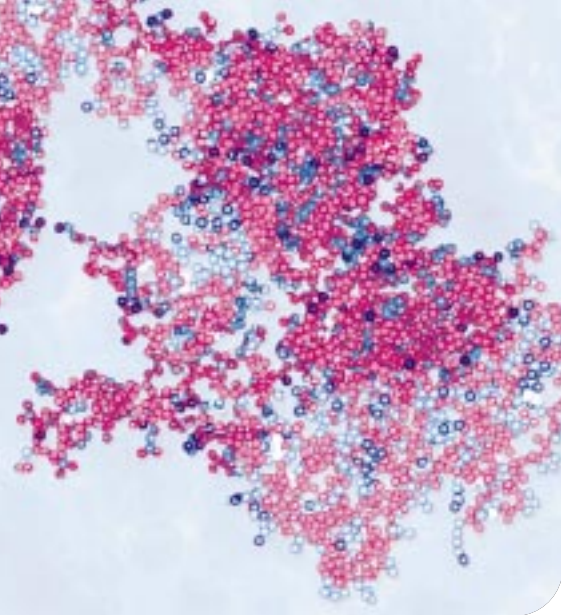
At the ASCO 2005 Annual Meeting, a joint analysis of the 2 trials, NSABP B-31 and NCCTG-N9831, was presented at a plenary session chaired by George Sledge, MD. Patients in the trastuzumab arms received weekly infusions of trastuzumab during or following completion of the paclitaxel phase of conventional AC-T chemotherapy (4 cycles of doxorubicin-cyclophosphamide over 3 months followed by 4 cycles of paclitaxel for 3 months). Analysis at a median of 2 years followup of 3351 participants showed that 3-year disease-free survival (DFS) was 87% in the trastuzumab arm vs 75% in the observation arm, a 52% relative reduction in breast cancer recurrence (hazard ratio [HR] = 0.48, $p < 0.0001$), accompanied by a 33% mortality reduction (HR = 0.67, $p = 0.015$).¹

At the same session Martine Piccart-Gebhart, MD, PhD presented the results of the Herceptin® Adjuvant Trial (HERA), a study coordinated by

the Breast international Group (BIG).² HERA treatment group participants received trastuzumab every 3 weeks following any approved adjuvant chemotherapy regimen, and the trial includes an arm taking trastuzumab for 2 years. In 3387 women followed for 1 year, 2-year DFS was 85.8% among the patients receiving trastuzumab vs 77.4% in those in the observation group, translating into a 46% reduction of recurrence (HR = 0.54, $p < 0.0001$). In all 3 trials, trastuzumab was given for a full year.

Prior efficacy in metastatic breast cancer

These results are more impressive in view of the data for trastuzumab in Stage IV metastatic breast cancer reported by Slamon et al in 2001,³ where the addition of trastuzumab to chemotherapy almost doubled time to disease progression from 4.6 to 7.4 months ($p < 0.001$), increased objective response from 32% to 50% ($p < 0.001$), reduced the 1-year death rate from 33% to 22% ($p = 0.008$) and prolonged median overall survival from 20.3 to 25.1 months ($p = 0.046$). As in another Stage IV study,⁴ the benefit of trastuzumab was restricted to



patients with positive HER2 status, either by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH analysis). FISH analysis, which detects amplification of the HER2 gene, has been found to be more predictive than expression by IHC.

Cardiac toxicity

Data from patients with metastatic disease has also revealed cardiac dysfunction (mainly congestive heart failure) to be an important side effect of trastuzumab, with a prohibitive 27% of patients affected when it is used in combination with the anthracycline doxorubicin. Combining trastuzumab with the taxane paclitaxel reduces cardiac dysfunction to 13%, compared to 1% when paclitaxel is given as monotherapy. Despite the documented cardiotoxicity, overall mortality in Stage IV disease was reduced by 20% in patients receiving trastuzumab. In the new adjuvant trastuzumab trials (NSABP B-31, NCCTG-N9831 and HERA), patients with preexisting cardiac disease were excluded from participation, and regular monitoring of left ventricular ejection fraction (LVEF) was done on all patients. In the joint NSABP B-31 and NCCTG study, Grade 3–4 cardiac toxicity was higher in the trastuzumab arms, 1% vs 4%. In the HERA trial, cardiotoxicity was less than 1%. Despite the cardiac side effect, overall mortality was reduced in all 3 studies.

Huge impact

The adjuvant trastuzumab data presented at this year's ASCO confirmed and magnified the results previously seen in advanced disease, creating an unstoppable "buzz" among investigators and

clinicians privy to the early news. Most centres began planning immediate change of their breast cancer care guidelines. Reasons to celebrate include the high recurrence reduction after adding a single drug, and the fact that the vast improvements are due to inactivation of a single molecule. It is a classic example of targeted therapy, the dream of the cancer establishment for decades.

If guidelines are changed, however, thousands of women across Canada will require costly and complex weekly or 3-weekly trastuzumab therapy soon after diagnosis, for a minimum duration of 1 year. This will entail a financial outlay of tens of millions of dollars by the provincial health systems. A concerted effort on an international scale regarding the best way to handle this type of decision-making is required, particularly as trastuzumab is only one of the targeted agents or biological therapies that are revolutionizing cancer management — all of them expensive and complex to administer (see box).

Determining cost–benefit

It is important that the formula for evaluating costs and benefits consider not only upfront expenditures but also subsequent savings due to avoiding otherwise-expected recurrences. The upfront cost in Canada of funding adjuvant trastuzumab, assuming a cost of \$C50,000 per patient for 1 year of treatment, and estimating that 15% of all newly-diagnosed patients with early Stage I–III breast cancer will be candidates (see box, page 10), would be over \$C160 million per year. Delayed dollar savings, however, will substantially offset the upfront price. The cost of 1 recurrence can be estimated at \$C70,000 for chemotherapy + \$C50,000 for trastuzumab given for metastatic disease, a total of \$C120,000 per patient. If adjuvant trastuzumab for early breast cancer can prevent more than 800 breast cancer recurrences each year, savings of 800 x \$C120,000, over \$C95 million, will be gained down the road — thus substantially lowering the cost of providing access to the drug from \$C160 million to \$C65 million per year. These estimates are applicable to regional, national or

Other targeted therapies for cancer

Already a reality in practice:

- **imatinib**, a tyrosine kinase inhibitor (TKI), is used in chronic lymphocytic leukemia (CLL) and gastrointestinal stromal tumour (GIST) stomach cancer.
- **rituximab**, an immunoglobulin monoclonal antibody, is used in a spectrum of B-cell lymphoproliferative disorders.

On the horizon:

- **bevacizumab**, an immunoglobulin monoclonal antibody and angiogenesis inhibitor, is showing benefits in Stage IV colorectal cancer⁵ and in breast cancer,⁶ and is being tested in adjuvant treatment for both tumour sites.
- **erlotinib** and **cetuximab**, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), are nearing regulatory approval for use in pancreatic and colorectal cancers, respectively.
- EGFR-TKI inhibitors **gefitinib** and **erlotinib** are effective in lung cancers with mutations of the EGF-1 receptor.
- Investigations are underway on other promising new agents combining EGF-1 and EGF-2 inhibition such as **lapatinib**⁷⁻¹⁰ and **sunitinib** (SU11248).¹¹⁻¹⁴

international budget projections, and indicate that the overall cost of giving adjuvant trastuzumab to most eligible HER2+ cases of early breast cancer is acceptable — and compares favourably with the cost–effectiveness profiles of other health programs already in place in Canada.

Eligibility criteria for trastuzumab in early breast cancer

According to guidelines in preparation in most parts of Canada, the U.S. and Europe, patients who are considered eligible for randomization in the trastuzumab adjuvant trials will be candidates, e.g. those with

- HER2+, node-positive disease unless ineligible due to cardiac dysfunction
- HER2+, node-negative disease unless the tumour is very low-risk (i.e. estrogen receptor-positive and tumour size < 2 cm or estrogen receptor-negative and tumour size < 1 cm) and/or cardiac dysfunction is present

In establishing eligibility guidelines for universal access, it is a concern that even women with seemingly low-risk disease have an identifiable risk of recurrence, as HER2 status is an independent adverse prognostic factor.¹⁵ As the benefit in reduction of events is evenly distributed across all prognostic subsets, adjuvant trastuzumab would result in about 4 avoided recurrences per 100 cases in the lowest-risk group of patients, who have an expected 8% probability of recurrence — a sizable absolute number that is meaningful to both patients and their treating physicians.


In the long run, the gains of not having to cope with recurrences will provide ultimate satisfaction to both clinicians and administrators, not to mention patients. It is important to appreciate that adjuvant trastuzumab means giving the drug earlier rather than later, and that giving it in the adjuvant setting could mean cures, while giving trastuzumab only at recurrence will fail to cure despite improving symptoms or scoring responses and prolonging survival.

HISTORIC EVENTS

The gains with adjuvant trastuzumab represent the largest improvement due to any therapeutic agent for human breast cancer ever recorded. Because of the very high rates of breast cancer in the population, implementing large-scale treatment with this agent will avoid big absolute numbers of breast cancer recurrences and save many lives.

Nonetheless, at the time of writing, approval of trastuzumab for adjuvant treatment of breast cancer has not yet been granted in many parts of Canada, although the same medication was approved for use in advanced metastatic disease several years ago. The delay is due to the perceived large cost.

Most provinces were caught off guard, without prior budget allocations for this type of program. Thus the potential benefit in avoiding a large number of breast cancer recurrences and eventual deaths cannot be fully realized at present. Due to concentrated efforts of the medical and lay breast cancer community, however, most Canadian provincial governments are rapidly regrouping their strategy for a positive approval in the near future.

The current situation, with targeted therapies achieving rapid advances in curability of malignancies in a number of sites — as exemplified here by trastuzumab — may be comparable to the era 60+ years ago when antibiotics were first used to successfully combat infections: cures for “incurable” diseases are on the horizon, potentially bringing human cancers and their therapy into the arena of therapeutic “miracles”. 

References

1. Romond E. Joint analysis of NSABP-B31 and NCCTG-N9831. Available at www.asco.org > Meetings and Education > Virtual Meeting > Advances in Monoclonal Antibody Therapy for Breast Cancer (Scientific Symposium, 2005). No abstract available.
2. Piccart-Gebhart MJ. HERA Trial. Available at www.asco.org > Meetings and Education > Virtual Meeting > Advances in Monoclonal Antibody Therapy for Breast Cancer (Scientific Symposium, 2005). No abstract available.

3. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *NEJM* 2001;344:783-92.
4. Seidman AD, Fornier MN, Esteva FJ et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001;19:2587-95.
5. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *NEJM* 2004;350:2335-42.
6. Miller K. E2100 Study. Available at www.asco.org > Meetings and Education > Virtual Meeting > Advances in Monoclonal Antibody Therapy for Breast Cancer (Scientific Symposium, 2005). No abstract available.
7. Spector NL, Xia W, Burris H et al. Study of the biologic effects of lapatinib, a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. *J Clin Oncol* 2005;23:2502-12.
8. Gomez HL, Chavez MA, Doval DC. A phase II, randomized trial using the small molecule tyrosine kinase inhibitor lapatinib as a first-line treatment in patients with FISH positive advanced or metastatic breast cancer. *Proc Am Soc Clin Oncol* 2005;23:203s. Abstract 3046.
9. Wülfing C, Machiels J, Richel D et al. A single arm, multicenter, open label, ph II study of lapatinib as 2L treatment of pts with locally advanced/metastatic transitional cell carcinoma (TCC) of the urothelial tract. *Proc Am Soc Clin Oncol* 2005;23:401s. Abstract 4594.
10. Fields AL, Rinaldi DA, Henderson CA et al. An Open-Label Multicenter Phase II Study of Oral Lapatinib (GW572016) as Single Agent, Second-Line Therapy in Patients with Metastatic Colorectal Cancer. *Proc Am Soc Clin Oncol* 2005;23:266s. Abstract 3583.
11. Fiedler W, Serve H, Dohner H et al. A phase 1 study of SU11248 in the treatment of patients with refractory or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease. *Blood* 2005;105:986-93.
12. Kulke M, Lenz HJ, Meropol NJ et al. A phase 2 study to evaluate the efficacy and safety of SU11248 in patients (pts) with unresectable neuroendocrine tumors (NETs). *Proc Am Soc Clin Oncol* 2005;23:310s. Abstract 4008.
13. Motzer RJ, Rini BI, Michaelson MD et al. Phase 2 trials of SU11248 show antitumor activity in second-line therapy for patients with metastatic renal cell carcinoma (RCC). *Proc Am Soc Clin Oncol* 2005;23:380s. Abstract 4508.
14. Demetri GD, van Oosterom AT, Blackstein M et al. Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of SU11248 in patients (pts) following failure of imatinib for metastatic GIST. *Proc Am Soc Clin Oncol* 2005;23:308s. Abstract 4000.
15. Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-82.

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