Efficacy of Trastuzumab as a single agent and combined with Paclitaxel or Docetaxel as treatment for HER2-positive breast cancer

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ABSTRACT

Breast cancer is a significant health condition in New Zealand; it is the most frequent cancer registration for females and contributes the largest proportion of female cancer deaths. Trastuzumab (Herceptin) has been proven to be an effective single agent against HER2-positive breast cancer showing a 26% response rate. More recently it has been shown that combining trastuzumab with chemotherapeutic agents such as docetaxel or paclitaxel (both taxane drugs) has an even greater effect with response rates of 61% and 36% respectively at one-year follow-up. Although trastuzumab does not usually show the adverse effects associated with chemotherapy it can cause cardiotoxicity although this can usually be reversed with careful management while continuing trastuzumab treatment. For New Zealand's HER2-posistive breast cancer patients Pharmac has decided to fund nine weeks of trastuzumab treatment combined with docetaxel.

INTRODUCTION

Breast cancer is the most common cancer for females comprising approximately a third of the total cancer registrations in New Zealand, second only to prostate cancer[1]. In 2003, 2325 women were diagnosed with breast cancer, accounting for 27% of female cancer registrations, and 647 women died[1]. The 2003 age-standardised registration rate for breast cancer was 81.5 per 100,000 female population, and this was 5.3% greater than the 1995 rate, but 8.4% less than the peak that occurred in 2000. The 2003 age-standardised mortality rate (20.7 per 100,000 female population) was 16.7% lower than in 1995[1].

Human epidermal growth factor receptor 2, known as cErbB2 or HER2, is one of four transmembrane tyrosine kinase receptors that mediate growth, survival and differentiation of cells[2]. The HER2 gene is amplified or the receptor over-expressed in approximately 15-25% of breast cancers[3], which is associated with aggressive tumour growth and a poor clinical outcome: shorter survival and decreased time to relapse[2,4]. This is because the over-expression of HER2 is an early pathogenic event in breast cancer and can lead to malignant transformation[5].

Trastuzumab is a recombinant monoclonal antibody that was developed from a murine antibody. The antibody is now 95% humanized to avoid patients developing neutralising antibodies against a murine protein. Trastuzumab has been developed to bind to the extracellular domain of HER2 expressed on cells. This causes a down-regulation of the p185ErbB2 protein and subsequent inhibition of downstream signalling, eventually leading to inhibition of ErbB2 cleavage and consequently decreased growth effects[6]. Thus Trastuzumab acts as an antagonist of Her2, inhibiting the growth-stimulating properties of the over-expressed HER2 protein and can stimulate antibody-dependent, cell-mediated responses[2]. Trastuzumab has been shown to produce a modest response as a single agent and impressive efficacy in combination with cytotoxic agent[6].

The biology of HER2 and trastuzumab

HER2-positive breast cancer is usually associated with increased expression of the anti-apoptosis protein Mcl-1, a member of the Bcl-2 family and is associated with survival of haematopoietic stem cells and lymphocytes. ErbB2-expressing cells upregulate the Mcl-1 protein and so these breast cancer cells are less likely to undergo programmed cell suicide[4]. With trastuzumab treatment this HER2 expression is reduced, corresponding to an increased sensitivity in these cells to apoptosis.

Nagata et al. (2004) investigated the effects that trastuzumab had on PTEN, an important protein in tumour suppression. PTEN is a phosphatase enzyme that is crucial in the recruitment of Akt activity. Akt is constitutively activated in HER2 overexpressing cells and is involved in tumour growth; PTEN expression inhibits Akt activity and therefore acts to limit tumour formation and growth[6].

Trastuzumab activates PTEN in breast cancer cells and this leads to rapid Akt dephosphorylation, contributing to the drugs antiproliferative effects[6]. PTEN deficiency was associated with a poor response to trastuzumab-based therapies, and so may be a useful predictor for resistance to this treatment. PTEN deficiency has been found in approximately 50% of breast cancers[6].

Trastuzumab as a single agent

Trastuzumab was shown to benefit patients with HER2 gene amplification in early phase I and II trials. Phase I trials assess the maximum tolerated dose and toxicity whereas phase II trials look primarily at efficacy and further evaluate toxicity. The efficacy of a chemotherapy regime can be measured using objective response rates (ORR), a combination of complete responses and partial responses. A complete response is the disappearance of all known disease for more than four weeks, and partial responses are considered to be a decrease in the sum of the perpendicular diameters of the present lesions of greater than 50% for more than four weeks with no new lesions. It is important to note that efficacy is more than just ORR, it also involves important aspects such as overall survival, quality of life and progression-free survival.

Vogel et al. (2002) investigated the efficacy of trastuzumab as a single agent and found an overall response rate of 26%[3]. Trastuzumab was found to be well tolerated, and was most effective when used to treat tumours that were more advanced. HER2 status was evaluated by immuno-histochemistry (IHC); a strong positive result (3+) is when greater than 10% of cells have complete membrane staining, reflecting an over-expression of the HER2 receptor[3]. If at least a moderate result (2+ or higher) was seen in IHC, Fluorescence In Situ Hybridization (FISH) analysis is used to look for gene amplification, this is the "gold standard" and would be checked in women before treatment was given.

Trastuzumab in combination with other cytotoxic agents

Trastuzumab is more effective in killing the cancer cells when combined with drugs that promote apoptosis. Trastuzumab treatment combined with a chemotherapy agent, for example paclitaxel, has a synergistic apoptotic response that involves inhibition of cell survival signalling pathways such as the Akt pathway[4,5,6]. This inhibition leads to a decrease in the expression of Mcl-1 protein thus rendering the cancer cell more vulnerable to apoptosis. Using cell culture techniques, studies showed that trastuzumab could increase apoptosis to between 30-40%[4].

Slamon et al. (2001) carried out a randomised controlled trial (RCT) that compared standard chemotherapy alone with trastuzumab combined with standard chemotherapy. The chemotherapy was paclitaxel unless the patient had never had any treatment before in which case it was doxorubicin. The trial randomised 234 patients to the standard chemotherapy regimen and 235 patients to the combination group[4]. The results (see Table 1) showed a large difference in overall survival (OS): the standard chemotherapy group had a median overall survival of eighteen months whereas the combination group was twenty-five months[7]. The striking difference in OS highlights the benefits from combining trastuzumab with paclitaxel when treating HER2-positive breast cancer[7].

More recently, Robert et al. (2006) built on the research by Slamon et al. by combining trastuzumab with paclitaxel (TP) treatment and compared it to the combination of trastuzumab, paclitaxel and carboplatin (TPC). The combination of paclitaxel and carboplatin has been used previously to treat solid tumours but is not used generally as a standard treatment for breast cancer[8]. In a multicentre phase III RCT, 196 women with tumours graded 2+ or 3+ for HER2 through IHC were assigned to receive either six cycles of TP or TPC.

The overall response rate for TP was 36% whereas the TPC regime was 59%, suggesting that carboplatin, a platinum agent, has an additive effect[8]. The TPC treatment resulted in improved progression-free survival (PFS) of thirteen months compared to eleven months for the TP group (see Table 1)[8].

Docetaxel, like paclitaxel, is a taxane and disrupts the microtubule functioning of a cell, thus limiting cell division. Clinical trials have shown a synergistic effect between trastuzumab and docetaxel[9]. Marty et al. (2005) conducted a multinational RCT comparing the response to docetaxel-only treatment against docetaxel and trastuzumab. A total of 188 women were randomly assigned into one of the two non-blinded groups; after 2 women dropped out of the study there were 94 in the docetaxel only group and 92 in the combination. This study showed an overall response rate of 61% in the trastuzumab/docetaxel regime compared to 34% in the docetaxel group (for further trial results see Table 1). After sensitivity analysis there was still a significant difference between the two treatment groups, where median progression-free survival was 31 months for the combination therapy, 8.5 months longer than the single therapy regimen[9].

The increased benefit in combining trastuzumab with docetaxel for HER2-positive breast cancers is similar to combining paclitaxel and trastuzumab, which is expected given they have similar mechanisms of action. Results from the separate trials are not directly comparable as there were different specifications set on eligibility of the women participating and what prior treatment they had received for their cancer. The size of each study on the efficacy of various combinations of HER2-positive breast cancer treatment was relatively small; greater certainty about the effect of treatments can be achieved through larger studies. However it may be unethical to randomise women to an observation-only course of treatment when studies completed so far have shown consistency in their results with trastuzumab treatment. Meta-analysis can be used to pool results of small trials, accepting that these may have different methods and eligibility criteria.

Baselga et al. (2006) pooled the data from four major adjuvant trials with a total population of over 13,000 women with HER2-positive breast cancer. Adjuvant therapy refers to additional treatment, usually given after surgery where all detectable disease has been removed, but where there remains a statistical risk of relapse due to disease that is not readily detectable. The pooled data were from the Herceptin adjuvant trial group (HERA), National Surgical Adjuvant Breast and Bowel project (NSABP), North Central Cancer Treatment Group (NCCTG) and the Breast Cancer International Research group (BCIRG). The analysis carried out on this population showed that patients treated with trastuzumab had a lower rate of 46-52% in risk of an event; relapse of distant metastasis, as compared to observation only patients[10]. The overall analysis also showed that the benefit seen was similar over the trials despite differences in chemotherapy regimes, sequencing of agents and patient populations. In the HERA trial, the hazard ratio for the risk of death with trastuzumab compared with observation alone was 0.66, which means there was a decreased risk of death by 34%, also an absolute disease-free survival benefit of 6.3% was seen at three years[11].

Safety of trastuzumab

Trastuzumab is a generally well-tolerated therapy and is not associated with the typical adverse effects from chemotherapies such as alopecia, myelosuppression or vomiting[6,10]. On the other hand, adverse effects such as chills, pyrexia, fatigue and headaches have been associated with trastuzumab and are more common at higher doses6. Cardiotoxicity is one of the most serious adverse effects of trastuzumab and was reported in 2-5% of women who received this as a single agent, however this was not indicated by preclinical or phase I studies[2,5,6]. An independent cardiac review committee performing retrospective analysis on a number of phase II and III trials found that increasing age and the combination of trastuzumab with an anthracycline, such as doxorubicin (which inhibits DNA and RNA synthesis) lead to a higher risk of cardiotoxicity[10]. Many hypotheses have been proposed to explain the cardiotoxicity seen with trastuzumab. These have included interactions between drugs, immune-mediated destruction of cardiomyocytes induced by the chemotherapy or the fact that the HER2 receptor is expressed on myocardium[12]. Most patients who develop any form of cardiac dysfunction are asymptomatic and there is a high level of reversibility of symptoms and left ventricle dysfunction[3,6,13]. Rates of trastuzumab discontinuation due to cardiac effects have been found to be low, less than 5%[11] however this should be the course of action if a patient develops congestive heart failure (CHF).

The pooled analysis of the four major adjuvant trials also looked at the incidence of cardiac events and found that they remained within acceptable levels. However, there was a higher incidence of CHF, as high as 3.3%, though this mostly responded well to treatment[10]. In the HERA analysis, at a one year follow up symptomatic CHF occurred in 1.7% of patients in the trastuzumab group compared to 0.06% in the non-trastuzumab patients receiving observation[10]. There has been no evidence of an increase in cumulative cardiotoxicity over one year, which is encouraging[11].

Most studies that investigated the efficacy of trastuzumab excluded women with a history of many cardiovascular conditions. This means that the effectiveness of trastuzumab in women with a pre-existing heart condition is unknown and it would be inadvisable to prescribe trastuzumab to this group of breast cancer patients.

CONCLUSION

There is no doubt that trastuzumab has improved the treatment of HER2-positive breast cancer patients, even though they are a minority of the total number of women with breast cancer. It improves the efficacy of

Study	Therapy regimen	Study size	Overall Response Rate	Overall Survival (median)
Vogel et al. (2002)	trastuzumab	114	26 %	24.4 months
Robert et al. (2006)	trastuzumab + paclitaxel trastuzumab + paclitaxel + carboplatin	98 98	36 % 52 %	32.2 months 35.7 months
Marty et al. (2005)	trastuzumab + docetaxel docetaxel	92 94	61 % 34 %	31.2 months 22.7 months
Slamon et al. (2001)	standard chemotherapy standard chemotherapy + trastuzumab	234 235	32% 50%	20.3 months 25.1 months

Table 1. Results of clinical studies on trastuzumab efficiency as a single agent and in combination with other therapies.

chemotherapy in this patient group with little additional toxicity, and represents a highly significant clinical advance in the care of women with breast cancer, however, it may not be appropriate for all patients because of existing cardiac morbidity.

Trastuzumab is effective on its own but combining it with another form of chemotherapy appears to have a greater benefit. In particular, trastuzumab used in conjunction with a taxane chemotherapy agent such as paclitaxel or docetaxel produces increased efficacy. This is most likely due to the favourable interaction that occurs between trastuzumab and the chemotherapy agent used. Trastuzumab treatment for a twelve-month period has been proven to have survival benefits in a significant proportion of women. However, more research into shorter treatment regimes, such as is being offered to breast cancer patients in New Zealand, may need to be completed to evaluate its efficacy. Nevertheless, there is definitely evidence to suggest that effective use of new developments such as trastuzumab will further reduce breast cancer deaths in New Zealand.

When advising a patient about trastuzumab, every case needs to be considered individually, but for many patients it seems likely that the efficacy of the treatment will outweigh the adverse effects associated. Eligibility of patients for trastuzumab treatment depends heavily on their cardiac function i.e. patients should have a left ventricular ejection fraction of at least 55%. Careful monitoring of each patient's cardiac function is necessary when being treated with trastuzumab and care should be taken in the event of developing adverse reactions. It is important to take into account that the addition of a second agent such as docetaxel or paclitaxel to trastuzumab will most likely increase the adverse effects. These include the more traditional adverse effects linked with chemotherapy such as alopecia, nausea and vomiting and would need to be taken into account when discussing treatment options that involve trastuzumab combination therapy for effective patient care.

REFERENCES

1. New Zealand Health Information Service.
Cancer: New Registrations and Deaths 2003. Anonymous. Anonymous. Wellington, NZ :
Ministry of Health. 2007.

2. Piccart-Gebhart, MJ., Procter, M., Leyland-Jones, B., Goldhirsch, A., et al.
Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.
N Eng J Med. 2005. 353: 1659-1672

3. Vogel, CL., Cobleigh, MA., Tripathy, D., Gutheil, JC., Harris, LN., Fehrenbacher, L., et al.
Efficacy and Safety of Trastuzumab as a single agent in first line treatment of HER2 over-expressing metastatic breast cancer.
J Clin Oncol. 2002. 20(3): 719 - 726

4. Henson, ES., Hu, X., Gibson, SB.
Herceptin Sensitizes ErbB2-Overexpressing Cells to Apoptosis by Reducing Anti-apoptotic Mcl-1 Expression.
Clinical Cancer Research. 2006. 12: 845 - 853

5. Baselga, J., Carbonell, X., Castaneda-Soto, NJ., Clemens, M., Green, M., Harvey, V., et al.
Phase II study of Efficacy, Safety and Pharmacokinetics of Trastuzumab Monotherapy Administered on a 3-weekly Schedule.
J Clin Oncol. 2005. 23: 2162 - 2171

6. Nagata Y., Lan, KH., Zhou, X., Tan, M., Esteva, FJ., Sahin, AA., et al.
PTEN activation contributes to tumour inhibition by trastuzumab and loss of PTEN predicts trastuzumab resistance in patients.
Cancer Cell. 2004. 6: 117 - 127

7. Slamon, DJ., Leyland-Jones, B., Shak, S., Fuchs, H., et al.
Use of Chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that over expresses HER2.
N Eng J Med. 2001. 344: 783-793

8. Robert, N., Leyland-Jones, B., Asmar, L., Belt, R., Ilegbodu, D., Loesch, D., et al.
Randomised Phase III Study of Trastuzumab, Paclitaxel and Carboplatin compared with Trastuzumab and Paclitaxel in Women with HER2 Over-expressing Metastatic Breast Cancer.
J Clin Oncol. 2006. 24: 2786 - 2792

9. Marty, M., Cognetti, F., Maraninchi, D., Snyder, R., Mauriac, L., Tubiana-Hulin, M., et al.
Randomized Phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with Human Epidermal Growth Factor Receptor 2-positive Metastatic Breast Cancer Administered as a first line treatment.
J Clin Oncol. 2005. 23: 4265 - 4274

10. Baselga, J., Perez, EA., Pienkowski, T., Bell, R.
Adjuvant Trastuzumab: A Milestone in the Treatment of HER-2-Positive Early Breast Cancer.
The Oncologist. 2006. 11(1): 4-12

11. Smith, I., Procter, M., Gelber, RD., Guillaume, S., Feyereislova, A., Dowsett, M., et al.
2-year follow up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial.
Lancet. 2007. 369: 29-36

12. Gonzalez-Angula, AM., Hortobágyi, GN., Esteva, FJ.
Adjuvant Therapy with Trastuzumab for HER2/neu-Positive Breast Cancerr.
The Oncologist. 2006. 11(8): 857-867

13. Suter, TM., Procter M., von Veldhuisen, DJ., Muscholl, M., Bergh, J., Carlomagno, C., et al.
Trastuzumab-Associated Cardiac Adverse Effects in the Herceptin Adjuvant Trial.
J Clin Oncol. 2007. 25(25): 3859-3865