Herceptin – from bedside to bench to clinic?

D.A. Cameron

NCRN Co-ordinating Centre, Arthington House, Cookridge Hospital, Leeds, UK

The 1980s saw a major research focus on newly discovered oncogenes, amongst which were the epidermal growth factor receptor (EGFR) and the chicken erythroblastoma protein, c-erbB2. They were recognised to be part of a family of cell surface proteins whose intracellular portion function as tyrosine kinases, activated when the receptors dimerise, usually in response to ligand binding. This particular family is now known as the human epidermal growth factor receptor family, and c-erbB2 or Her-2 *neu* is now more widely known as HER-2, and is overexpressed/amplified in between 20% and 30% of invasive human breast cancers [1]. The worse prognosis associated with these so called 'HER2-positive' was quickly recognised, and our understanding of their natural history has grown rapidly since [2].

There are data to suggest that HER2 may also be an important predictive factor of response to chemotherapy and hormonal therapy [3]. HER2 overexpression is usually caused by amplification of the HER2 gene [4], which leads to increased levels of HER2 mRNA and increased expression of the HER2 protein on the tumour cell surface [5]. HER2 gene amplification occurs early in the development of breast tumours and is maintained throughout the course of the disease. It can occur in almost any breast cancer, though is more common in cancers with other poor prognostic markers such as the absence of hormone receptors, high grade etc. Recently it has also become clear that patients with HER2 overexpressing breast cancer have a high risk of developing central nervous system disease – up to one third or more patients with metastatic disease will have this devastating complication.

Herceptin

Although HER2 overexpressing cancers have a worse prognosis, it is in fact the possibility of using trastuzumab (Herceptin®) that is the main justification for knowing the HER2 status of a patient's breast cancer. Herceptin is a biologically engineered, humanised immunoglobulin-1 (IgG1) targeted against the HER2 extracellular domain, made with the hypervariable antigen-binding regions of a potent murine anti-HER2 monoclonal antibody (muMAb 4D5) grafted into a human IgG framework without loss of specificity. *In vitro* it has been shown to have marked inhibition of the growth of breast and other cancer cell lines [6].It is not clear exactly how it works, but it is potentially antiproliferative, can recruit the immune system leading to antibody-dependent cell-mediated cytotoxicity, and accelerate the degradation of the HER2 receptor (see [7,8]).

The benefit for patients of this monoclonal antibody was first demonstrated in women with HER2 positive metastatic breast cancer. Single agent response rates are around 35%, but the most dramatic benefits were seen in trials where Herceptin was combined with standard chemotherapies used in the treatment of metastatic breast cancer [9]. Early studies and pharmacokinetic modelling suggested a 6–7 day half-life, leading to weekly schedules. More recently, it has become clear that the true half-life is at least 3 weeks, so that this is becoming the standard schedule for administration, particularly once steady state levels have been achieved.

Toxicity

Herceptin is generally very well tolerated, with the most commonly reported adverse events being mild-to-moderate infusion-related reactions, which occurred in around 40% of patients. These reactions were mostly associated with the first infusion, did not lead to interruption of the infusion, and resolved with standard treatment. Haematological toxicities commonly seen with chemotherapy, such as neutropenia, anaemia and thrombocytopenia, were uncommon following Herceptin monotherapy, though it is possible that their frequency is slightly increased by the concomitant administration of chemotherapy and Herceptin.

The biggest problem was the unexpected risk of cardiac events. This has led to a need to monitor cardiac function in patients receiving Herceptin, but

further research has led to the understanding that much of the cardiac toxicity seen with the use of Herceptin is due to Herceptin's impact on the ability of the myocardium to repair cardiac damage from other causes, most commonly anthracycline chemotherapy. The overall risk remains low in current practise, and analysis of data pooled from six phase II and III trials with a total of 629 patients (418 of whom received Herceptin) showed that the incidence of clinically significant cardiac events (congestive heart failure) in patients who received Herceptin was only 2.7%, and an even lower rate has been reported in some of the adjuvant studies.

Clinical trials in early breast cancer

Five studies have confirmed the benefit of giving adjuvant Herceptin to HER2 overexpressing breast cancer, even with a median follow-up of only 2–3 years. Furthermore, this reduction in relapse translates into an overall survival gain of around 33% for the patients could improve disease-free survival, as confirmed by the joint analysis of the N9831 & NSABP B-31 studies and the 2 year report of the HERA trial. What is less clear is the optimal regimen. The HERA trial gave all the Herceptin after chemotherapy, whereas all the others combined it with taxane-based treatment. Neither is the optimal duration known: the FINHER trial demonstrated the same magnitude of benefit with only 9 weeks use. Finally, the BCIRG trial had an arm with Herceptin but no anthracycline, and the latest update appears to show no significant difference in outcome from the arm with both Herceptin and anthracyclines. Further trials are underway to try and answer some of these questions, as well as others looking to confirm the high pathological response rate seen when the chemotherapy and Herceptin are given before surgery [10–13].

Research is also being conducted to identify the subgroup of patients who really benefit from Herceptin, building on the intriguing data presented at the 2005 San Antonio Breast Cancer conference from the NSABP B-31 trial, which reported that the reduction in hazard ratio for recurrence was 76% in tumours with mutations in the c-myc oncogene, but only 37% in those without.

Other anti-HER2 approaches

The success of Herceptin establishes the HER2 protein as a key therapeutic target, and a number of other drugs are in development. The most developed is lapatinib, a small molecule dual EGFR/HER2 inhibitor. It has shown single agent activity at a level similar to Herceptin, and has been shown to approximately halve the hazard ratio for time to progression when added to capecitabine in women with advanced disease that has become resistant to anthracyclines, taxanes and Herceptin [14]. There was even a suggestion that fewer women developed CNS involvement at their time of progression – which if confirmed with further follow-up gives some hope for this devastating complication of HER2 overexpressing metastatic disease.

This efficacy has led to a number of further trials being conducted, both in advanced and early breast cancer. No further key clinical data are expected before the end of 2007, but some parallel translational studies with the tumours of patients in the lapatinib trials have been conducted and they may give us insights as to the benefit of lapatinib: the key question is whether it will be as good as, or even superior to Herceptin. In terms of cardiac toxicity it appears at this stage to be associated with a lower frequency of clinically significant damage.

Conclusion

It is down to the success of modern molecular biology and the co-operative approach in current clinical trials that it took only 21 years from the first report of an antibody successfully targeting a member of the HER family of tyrosine kinases, to the demonstration of a survival advantage for the adjuvant use of a similar antibody in early breast cancer. Novel anti-HER2 agents are now being developed – all of us hope that the same powerful molecular and clinical research paradigms will deliver even more effective treatments for those patients who still die from this sub-type of breast cancer.

Conflict of interest statement

The author has received honoraria and advisory board payments from both Roche and GSK.

References

1 Owens MA, Horten BC, Da Silva MM, *et al.* HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. *Clin Breast Cancer* 2004, **5**, 63–69.
2 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**, 177–182.
3 Lohrisch C, Piccart M. HER2/neu as a predictive factor in breast cancer. *Clin Breast Cancer* 2001, **2**, 129–135.
4 Pauletti G, Godolphin W, Press MF, *et al.* Detection and quantification of HER-2/neu gene amplification in human

breast cancer and archival material using fluorescence in situ hybridisation. *Oncogene* 1996, **13**, 63–72.
5 Hynes NE, Gerber HA, Saurer S, *et al.* Overexpression of the c-erbB-2 protein in human breast tumor cell lines. *J Cell Biochem* 1989, **39**, 167–173.
6 Motoyama AB, Hynes NE, Lane HA. The efficacy of ErbB receptor-targeted anticancer therapeutics is influenced by the availability of epidermal growth factor-related peptides. *Cancer Research* 2002, **62**, 3151–3158.
7 Gennari R, Menard S, Fagnoni F, *et al.* Pilot study of the mechanism of action of preoperative trastuzumab in patients with primary operable breast tumors overexpressing HER2. *Clin Cancer Res* 2004, **10**, 5650–5655.
8 Molina MA, Codony-Servat J, Albanell J, *et al.* Trastuzumab (Herceptin), a humanized anti-HER2 receptor monoclonal antibody, inhibits basal and activated HER2 ectodomain cleavage in breast cancer cells. *Cancer Res* 2001, **61**, 4744–4749.
9 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. *New Eng J Med* 2001, **34**, 783–792.
10 Romond EH, Perez EA, Bryant J, *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New Eng J Med* 2005, **353**, 1673–1685.
11 Piccart-Gebhart MJ, Procter M, Leyland-Jones B, *et al.* Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER-2 positive breast cancer. *N Engl J Med* 2005, **353**, 1659–1672.
12 Joensuu H, Kellokumpu-Lehtinen PL, Bono P, *et al.* Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 2006, **354**, 809–820.
13 Slamon D, Eiermann W, Robert N, *et al.* Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: Second interim efficacy analysis. Presented at SABCS; December 2006 [available at www.cirg.org].
14 Geyer CE, Forster J, Lindquist D, *et al.* Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *New England Journal of Medicine* 2006, **355**, 2733–2743.