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Herceptin® – from laboratory to cure in breast cancer?

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ABSTRACT There has been considerable publicity surrounding the potential benefits of herceptin in treating early breast cancer and whether or not its benefits outweigh the costs of treatment. In this article, requested by visitors to the www.behindthemedicalheadlines.com site, Dr David Cameron provides an overview of the development of herceptin, its use in treatment and its safety profile.

KEYWORDS Breast cancer, HER2, Herceptin®, trastuzumab

LIST OF ABBREVIATIONS Breast Cancer International Research Group (BCIRG), epidermal growth factor receptor (EGFR), Herceptin® Adjuvant Trial (HERA), immunoglobulin-1 (IgG1), left ventricular ejection fraction (LVEF)

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Breast cancer remains the second most common cancer in the world (after lung cancer), and a major cause of cancer-related death in women. More than forty thousand new cases of breast cancer are diagnosed each year in the UK, and around 9% of women will develop the disease during their lifetime. Whilst there have been huge improvements over the past 20 years in the survival rate for women with early breast cancer (that which has not obviously metastasised at presentation), unfortunately around one third of all patients will develop recurrent disease despite primary treatment. For those who relapse in a site distant from the breast, the survival time has also improved, but only a minority will live for more than five years from the time of diagnosis of metastatic breast cancer.

HER2-POSITIVE BREAST CANCER

In the 1980s, many laboratories worked on newly discovered oncogenes, amongst which were the EGFR and the chicken erythroblastoma protein, *c-erbB2*. These were recognised to be part of a family of cell surface proteins whose intracellular portions function as tyrosine kinases, activated when the receptors dimerise, usually in response to ligand binding. The family is known as the human epidermal growth factor receptor family, and *c-erbB2* or *HER2* neu is now more widely known as *HER2*, and is over-expressed/amplified in about 20% to 30% of invasive human breast cancers.[1] These so-called 'HER2-positive' breast cancers are an aggressive form of the disease with poor prognosis, including high risk of recurrence, metastasis and reduced overall survival.[2]

In the clinic, there are data to suggest that HER2 may also be an important predictive factor of response to chemotherapy and hormonal therapy in breast cancer.[3] Therefore, testing to establish the HER2 status of tumours from women with breast cancer has been incorporated into routine clinical practice to assist prognosis and prediction of treatment response, and more recently, the possibility of using adjuvant Herceptin®. HER2 over-expression 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.

HERCEPTIN®

Herceptin® is a biologically engineered, humanised 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, gastric and ovarian cancer cell lines.[6] Its exact mechanism of action is not clear, but potential mechanisms include direct antiproliferative effects, recruitment of the immune system leading to antibody-dependent cell-mediated cytotoxicity[7] and acceleration of the degradation of HER2 through internalisation from the cell membrane. It is also possible that by binding to the external part of the receptor, this stops cleavage of this part of the HER2 receptor by metalloproteinases, thus preventing

homodimerisation of the truncated HER2 which would lead to constitutive growth signalling.[8]

USE OF HERCEPTIN® IN METASTATIC BREAST CANCER

The benefit for patients of this monoclonal antibody was first demonstrated in women with HER2 positive metastatic breast cancer. In studies of this drug given as a single agent therapy, response rates of up to 35% were seen. Such rates are not very different from those expected from the use of a chemotherapeutic agent or hormone drug when given alone. However, the most dramatic benefits were seen in trials where Herceptin® was combined with standard chemotherapies used in the treatment of metastatic breast cancer. The first trial randomised 469 women with HER2 positive metastatic breast cancer to either standard chemotherapy alone (with Herceptin® being made available when the disease subsequently progressed), and the combination of the same chemotherapy and Herceptin®.[9] Not only was there a significant improvement in tumour response rate and time to disease progression for those women given Herceptin® with chemotherapy, but this led to a clear improvement in median survival by more than six months. Trials reporting a significant survival advantage for one regimen over another in advanced breast cancer are not common: this one was even more remarkable in that the patients had a poor prognosis by virtue of their tumours over-expressing HER2.

Following this study, a similar study was conducted using another widely prescribed drug, Taxotere, and it too reported a survival advantage for the combination of Herceptin® plus chemotherapy. Therefore the combination of taxane plus Herceptin® is becoming the standard of care for women with HER2-positive advanced breast cancer. It remains unclear whether Herceptin® should be continued once there is a need for another chemotherapeutic agent. There is some evidence from retrospective analyses and an extension study indicating that continuation of Herceptin® beyond disease progression is well tolerated and possibly beneficial. At present there are no randomised data to confirm this, but it has become standard practice in many countries, especially the USA.

The early studies and pharmacokinetic modelling suggested a six to seven day half-life, leading to weekly schedules. More recently, it has become clear that the true half-life is at least three weeks, so that this is becoming the standard schedule for administration, particularly once steady-state levels have been achieved.

SAFETY AND ADVERSE EFFECTS

The safety profile of Herceptin® was established in these two early pivotal clinical trials. No new or unexpected adverse events associated with Herceptin® have been reported since these trials were conducted.

Herceptin® is generally very well tolerated, and is not associated with the adverse effects usually observed with chemotherapy, such as nausea, vomiting, alopecia and mucositis. The most commonly reported adverse events were 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®.

Serious infusion-related reactions are rare, but are characterised by respiratory symptoms, such as dyspnoea, bronchospasm and respiratory distress, and may be accompanied by an anaphylactoid reaction with hypotension and rash. These symptoms generally appear within two hours following the start of the first Herceptin® infusion, and they can be managed through cessation of infusion, treatment with antihistamines, corticosteroids and beta-antagonists, and administration of oxygen. Administration of further infusions of Herceptin® to patients who experienced serious infusion-related reactions has not been associated with recurrence of the reactions. Patients who are at risk of developing severe infusion-related reactions can be identified before initiation of treatment. In a post-marketing analysis in early 2000, there were nine reports of infusion-related deaths (within 24 hours of Herceptin® administration) amongst 25,000 patients given Herceptin® for advanced breast cancer. Most of the nine patients with fatal infusion-related reactions had significant pre-existing pulmonary compromise secondary to advanced malignancy, and several of these patients were on supportive oxygen therapy at the time of their first Herceptin® infusion. Such patients would now be more cautiously treated with Herceptin®.

CARDIAC TOXICITIES

It has been widely reported that Herceptin® has been associated with an increased risk of cardiac events. This was not expected from pre-clinical toxicology studies, and was most common in patients given Herceptin® in combination with anthracyclines, something that is no longer done outside clinical trials.

Most patients who developed cardiac dysfunction in the early studies were symptomatic, and most (79%) improved with standard treatment for congestive heart failure.

Trial	No.	Design	Median Follow-up	HR for DFS	HR for OS	Cardiac Toxicity
N9831 + NSABP B-31	3,351	AC → P ±H	24 months	**0·48**	**0·67**	**3·3%** **4·1%**
N9831	1,964	AC → P → ±H	18 months	*0·87*	*0·85*	**2·2%**
HERA	3,387	Chemo → ±H	12 months 24 months	**0·54** **0·64**	*0·76* **0·66**	**2·3%**
BCIRG 006	2,147 2,148	AC → T ±H CarboTH	23 months	**0·49** **0·61**	*36 vs 20* *36 vs 28*	**2%** *0·5%*
FinHer	231	T(V)H → FEC	36 months	**0·43**		*0%*

TABLE 1 Summary of the five adjuvant Herceptin® trials reported to date.
- All Herceptin® was given for 1 year, except for Finher where it was only for 9 weeks.
- Non-significant differences are shown in italics.
- Control arm patients are counted twice for N9831 and BCIRG 006, as two different analyses of treatment are presented.
- Cardiac toxicity includes cardiac death, grade 3/4 cardiac failure, but NOT arrythmias (as data on arrythmias only available for BCIRG006).
- Control arm cardiotoxicity rates were all around 0·1% – 0·3%.
- AC (Adriamycin + Cyclophosphamide).
- P (Paclitaxel).
- CarboTH (Carboplatin +Taxotere with Herceptin® starting with the first cycle of chemotherapy).
- T (Taxotere) V (Vinorelbine) FEC (5-FU, Epirubicin, Cyclophosphamide).
- AC→P±H means AC chemotherapy followed by Paclitaxel with patients randomised to commence (or not) Herceptin® with the paclitaxel.
- AC→P →±H means AC chemotherapy followed by Paclitaxel with patients randomised to commence (or not) Herceptin® after the paclitaxel.

All patients should be assessed for risk factors for cardiac disease before they receive Herceptin®. Also, evaluation of LVEF should be performed before and during Herceptin® therapy. Such prospective cardiac monitoring has been included in Herceptin® trials conducted after the pivotal combination trial. Analysis of data pooled from six phase II and III Herceptin® trials comprising 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%.

DRUG INTERACTIONS

Drug interaction studies have not been conducted for Herceptin®. No interaction has been reported between Herceptin® and the two currently used taxanes, docetaxel and paclitaxel, nor with the currently widely used hormonal agents.

CLINICAL TRIALS IN EARLY BREAST CANCER

The survival benefits seen with the use of Herceptin® in advanced breast cancer led investigators to consider the possibility that use of Herceptin® in patients with curable breast cancer could add to the improvements in survival already achieved with current hormonal therapies and chemotherapies.

Five studies have been conducted testing the hypothesis that the use of Herceptin® in HER2 over-expressing early breast cancer could improve disease-free survival. At between one and three years' follow-up, the first reports from all these trials demonstrated that the use of Herceptin® approximately halved the risk of recurrence of this high-risk type of early breast cancer (see Table 1).

However, these trials were not identical in design, and their differences have posed as many questions as they have answered. Firstly, the three studies based in North America (N9831, NSABP B-31[10] and BCIRG 006) built on the data from the taxane–Herceptin® combination in advanced breast cancer, proscribed a standard anthracycline–taxane chemotherapy sequence and started the Herceptin® with the taxane, continuing to a total of one year. The HERceptin® Adjuvant trial, that recruited from most of the rest of the world, tested the benefit of one year's Herceptin® when given as a single agent after completion of all standard chemotherapy and radiotherapy, and contains a third arm as yet unreported where the Herceptin® was given for a total of two years.[11] The N9831 trial had a third arm where the Herceptin® was still given for one year, but starting after the chemotherapy as in the HERA trial. In the early analysis of N9831 this last arm appeared much less effective, yet in the HERA trial it was still associated with almost a halving of the recurrence rate. The BCIRG trial also

tested the novel schedule of a platinum–taxane–Herceptin® combination, based on strong evidence for synergy in pre-clinical studies. Preliminary results from this trial do not confirm that this is the best arm, and suggest that it might be slightly inferior to the anthracycline–taxane–Herceptin® arm.

A provocative study has recently been reported from Finland. Within a randomised adjuvant chemotherapy study, the 231 women who had HER2-positive breast cancer were also randomised to receive (or not) Herceptin® immediately after surgery concomitantly with the non-anthracycline part of their chemotherapy. These women, given Herceptin® for only nine weeks, similarly had a halving of the risk of recurrence, resulting in those women with HER2-positive breast cancer receiving Herceptin® having the same prognosis as those with HER2-negative breast cancer included in the same study.[12]

When all these studies were released last year, there was concern expressed that the data were too immature and that no survival advantage would be seen. In fact the combined analysis of the two US trials, N9831 and NSABP B-31, had already reported a 33% improvement in survival after a median follow-up of two years, and in 2006 it was reported that with an additional year's follow-up, the HERA trial is seeing a similar (34%) improvement in overall survival.

More than 13,000 women have been randomised within these trials, and they all confirm that the use of Herceptin® approximately halves the risk of recurrence for those patients with high-risk HER2-positive early breast cancer. The Finnish study raises the possibility that nine weeks of treatment given immediately after surgery and combined with chemotherapy is as effective as one year's treatment. The HERA trial two-year arm remains unblinded, so it is not known if a longer or shorter duration is appropriate.

As with all 'targeted' therapies, there remains the question as to whether it is possible to further narrow down the group of women who gain most from the use of Herceptin®, in order to minimise financial and toxicity 'costs' whilst maximising patient benefits. Data from the adjuvant trials currently do not point to traditional prognostic factors being helpful, with no significant differences in the relative benefit according to node or Oestrogen receptor status. However the answer probably lies in the biology, not pathology, of the cancer, as suggested by data presented at the 2005 San Antonio Breast Cancer conference from the NSABP B-31 trial. Analysis of the primary tumours in that study indicated 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. The absolute gains (and thus cost-effectiveness) do of course differ according to overall prognosis.

Close cardiac monitoring occurred in all these studies, and patients with any significant cardiac history or abnormal baseline left ventricular function were excluded. The data to date are very re-assuring, with between 0 and 4·1% of patients developing clinical heart failure, no cardiac deaths, and the majority of patients recovering with appropriate therapy. Cumulative incidence curves strongly indicate that the risk of heart failure is only higher whilst receiving Herceptin®, and once stopped, patients are at no greater risk than those given the same chemotherapy without Herceptin®. It must be acknowledged however that it is not known if patients given adjuvant Herceptin® have any long-term increase in risk of cardiac disease.

OTHER TUMOUR TYPES

Breast cancer is not the only disease to over-express the HER2 protein, and therefore clinical trials have been conducted in a number of other malignancies, including pancreatic, oesophageal, hormone-refractory prostate cancer, non-small-cell lung cancer and ovarian cancer. None of these studies have reported significant activity, leaving open the question as to whether HER2 is uniquely functionally over-expressed in breast cancer, or the possibility that the biology is different in these other tumours (as hinted at by the greater apparent efficacy seen in ovarian cancer for a different HER2 targeted antibody, pertuzumab). The one other tumour type where there is currently an active trial programme is gastric cancer.

HEALTH ECONOMICS

It has been estimated that it will cost the NHS between £25,000 and £30,000 per patient treated with Herceptin® for early breast cancer. Some have asked if this is affordable, and whether it meets standard cost-effectiveness criteria. The Scottish Medicines' Consortium, which rigorously appraises the clinical and cost-effectiveness data, has deemed it suitable for use within the NHS in Scotland, and NICE has issued similar provisional guidance for England and Wales. Since these are independent bodies, this gives strong support to the notion that this cost is justified by the clinical benefits seen.

CONCLUSION

It was only 21 years from the first report of an antibody successfully targeting *in vitro* a member of the EGFR or HER family of tyrosine kinases, to the demonstration of a survival advantage for the use of a similar antibody (but against HER2) in the adjuvant therapy of early breast cancer. Whilst lessons have been learnt along the way, and a modest but unexpected cardiac toxicity was seen, this represents one of the best examples of how science can lead to significantly better chances of cure in a common solid cancer.

KEYPOINTS

- Herceptin® is a humanised immunoglobulin directed against the epidermal growth factor receptor (HER2).
- HER2 is over-expressed in up to 30% of invasive breast cancers.
- *In vitro* Herceptin® inhibits growth of breast, gastric and ovarian cancer cell lines.
- Clinical trials suggest that Herceptin® halves the risk of recurrence in high-risk HER2-positive early breast cancer.
- Side effects include cardiac toxicity, acute anaphylaxis and pulmonary reactions in some patients.
- The place of Herceptin® in breast cancer treatment is being clarified through ongoing clinical trials.

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