Herceptin: Is it really worth it?

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Canada's ailing healthcare system has been dealt another blow with the expensive and potentially lifesaving drug Herceptin®. The issues at stake question fundamental aspects of the Canadian healthcare system and raise ethical questions which have obvious answers but are difficult to implement. Herceptin® was approved in 1998 by the Food and Drug Administration and is being used on its own as a single agent or with conventional chemotherapy, specifically paclitaxel in treating HER2/neu-overexpression or HER2/neu-positive metastatic breast cancer (MBC) (Willems, Gauger, Henrichs, & Harbeck, 2005). This article discusses the effectiveness and costs of Herceptin®.

How does Herceptin® work?

In normal cells, the human epidermal growth factor receptor-2/neu (HER2/neu) protein functions in regulating cellular growth and division. The HER2/neu protein is encoded by the cellular-erB-2 proto-oncogene (Bianco, 2004; Sahin, 2000). More specifically, the protein is a 185-kDa transmembrane tyrosine kinase receptor (Emens, 2005; Ross et al., 2004). Around 25-30% of breast cancers are caused by an overexpression of the HER2/neu protein (FDA, 2005). Whereas a non-cancerous breast cell would have two copies of the HER2/neu gene, the number of HER2/neu gene copies is elevated in women with HER2/neu-positive breast cancer. This leads to a higher density of the HER2/neu protein on the cell surface, which causes increased cellular division forming a tumor. Unfortunately, being a more aggressive form of cancer with shorter survival rates, HER2/neu-positive breast cancer is associated with a poor prognosis (Altundag, Esteva, & Arun, 2005; Emens, 2005).

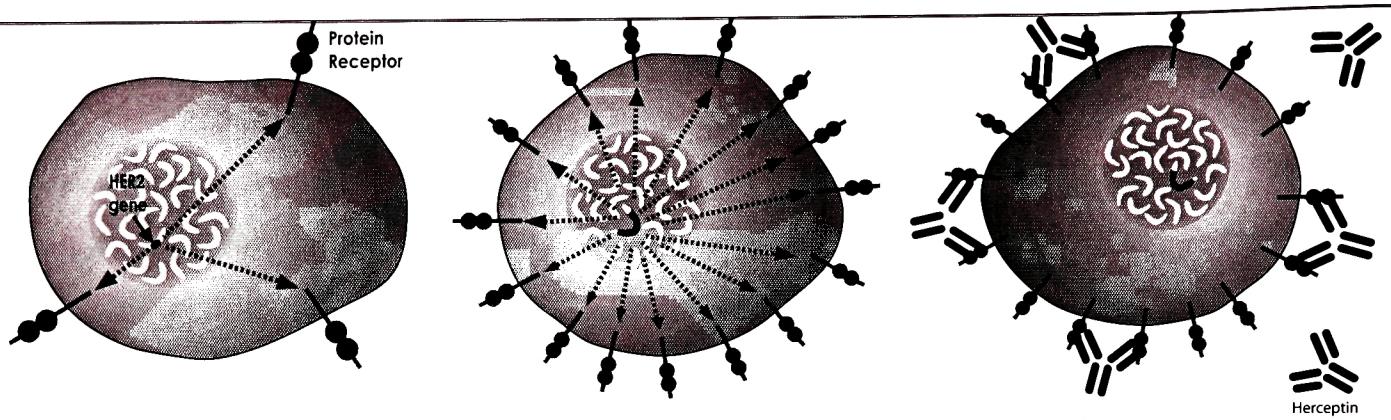
Herceptin® is the brand name for trastuzumab, which is a human-murine recombinant DNA-derived anti-HER2 monoclonal antibody (FDA, 2005). Herceptin® falls into the category of a biological therapy, since it is derived from living cells. Administered intravenously, it is used in targeted drug delivery for the treatment of HER2/neu-positive metastatic breast cancers (FDA, 2005; Yarden, Baselga, & Miles, 2004). Pharmacodiagnostic tools have shown that Herceptin® has a high affinity for the HER2/neu protein's extracellular domain (see Figure 1). Binding of Herceptin® inhibits further proliferation of HER2/neu-positive tumor cells by interfering with associated intracellular signals (FDA, 2005). The effects of Herceptin® may also be due to its ability to facilitate antibody-dependent cellular mediated cytotoxicity, which would involve the host's immune system (FDA, 2005).

Herceptin® should only be administered once HER2/neu overexpression has been confirmed (Bilous et al., 2003). This can be diagnosed using either immunohistochemistry, which detects overexpression of the protein itself, or fluorescence in situ hybridization, which detects gene amplification (Willems et al., 2005; Ross et al., 2004). Herceptin® was identified using pharmacogenomics, which is the study of how an individual's genotype relates to that individual's response to a particular drug. More specifically, pharmacogenomics analyzes specific genetic alterations which, in the case of cancer, can be inherited from one generation of cancerous cells to the next (Bartlett, 2005). The overexpression of the HER2/neu protein or amplification of the HER2/neu gene is an example of a specific genetic alteration that transforms normal breast cells into cancerous ones (Yarden, Baselga, & Miles, 2004).

Assessing the Efficacy of Herceptin®

There are currently other breast cancer biological therapeutic drugs available on the market. Since Herceptin® is a relatively new treatment, it is important to report clinical trials that have assessed its efficacy. All patients involved in the Herceptin® clinical trials have been HER2/neu-overexpressing MBC patients. Clinical trials of Herceptin® have looked at, among other things, its effect on disease progression, the rate of death, and the reduced risk of death (Slamon et al., 2001; O'Shaughnessy, 2005).

Until recently, traditional chemotherapy was the



Normal Cell

In normal breast tissue cells, the HER2 gene produces a protein receptor on the cell surface. These growth factor-like receptors are thought to play a role in normal cell growth by signaling the cell to divide and multiply.

HER2 Overexpressing Cancer Cell

Cancerous breast tissue cells that overexpress (or overproduce) the HER2 gene produce extra protein receptors on the cell surface. The higher density of receptors triggers the cell to divide and multiply at an accelerated rate, thus contributing to tumor growth. Approximately 25-30% of all women with metastatic breast cancer overexpress the HER2 protein.

Herceptin® (Trastuzumab)

It is thought that Herceptin (a HER2 antibody) binds to numerous HER2 receptor sites found on the cell surface, blocking the receptor sites and possibly preventing further growth by interrupting the growth signal. As a result, the HER2 antibody may slow progression of the disease.

Figure 1: Comparing various HER2/NEU expression and Herceptin® binding (www.gene.com).

standard treatment for HER2/neu-overexpressing MBC. With the development of Herceptin®, however, this may change. Where chemotherapy has been used on its own to treat HER2/neu-overexpressing MBC, the results have not been very positive. Full treatment response rarely occurs and partial treatment response only occurs in 35 to 40% of patients (Nahleh & Jazieh, 2005). On average the survival time can vary from 18 to 30 months with the latter corresponding to, in most cases, those who respond well to treatment (Nahleh & Jazieh, 2005). On the other hand, studies have demonstrated the efficacy of Herceptin® when it is used on its own. One study conducted out of the Vall d'Hebron University Hospital in Barcelona, Spain, showed a 19% overall response rate to Herceptin® on average (Ardavanis et al., 2005).

In most of the current studies, Herceptin® is often administered in conjunction with chemotherapy to determine any improvements. It appears that in conjuction with chemotherapy, Herceptin® demonstrates synergistic anti-tumor activity that is greater than when used alone (Emens, 2005; Emens & Davidson, 2004; Adams & Weiner, 2005). According to a study published in *The Indian Journal of Pediatrics,* use of traditional adriamycin or taxol based chemotherapy produced an average survival time of 20 months but with the addition of Herceptin®, survival time increased to 29 months (Mohindru, 2005).

Another study found that there was a higher survival period, 25.1 months, for patients that were administered both Herceptin® and chemotherapy, compared to survival of 20.3 months for patients only on traditional chemotherapy. The same study also showed that disease progression was delayed by an average of 3 months for those on Herceptin® and chemotherapy (Slamon et al., 2001). In a study conducted by the U.S. National Cancer Institute, there was a 52% decrease in disease recurrence and a 33% reduction in death with regard to patients on this combined method of treatment (U.S. National Institutes of Health, 2005).

Although there seem to be many positive aspects of Herceptin, a common side effect in various studies has generated a lot of concern: the relative cardiotoxicity of the treatment. It has been shown that a combination of chemotherapy agents (specifically anthracycline and adriamycin) with Herceptin® lead to a 26% increase in cardiotoxicity and congestive heart failure (Mohindru, 2005). Similarly, in another study, cardiac dysfunction due to an increase of cardiotoxicity was the major drawback that appeared in experimental treatments (see Table 1).

Our Healthcare System and Herceptin®

Fundamentally, the main concern with Herceptin® is the associated cost. It costs more than $35,000 to treat one patient (Kinner, 2005). The steep price for this drug is a result of the average $1.7 billion that is required to put new drugs on the market, according to the Bain report released in 2005 (Gilbert & Rosenberg, 2004). To make a return on the investment, drug companies must charge high market-based prices which lead to expensive treatments like Genentech's Herceptin®. As more drugs are tailored for specific strains of cancer, higher costs should be expected. Reduction in costs would require different economic principles, one in which drug development would be less of a private enterprise and more of a public service.

Although Herceptin® was approved for use by Health Canada in 1999, concrete national financing schemes have yet to appear. Both the federal and provincial governments have been hesitant because of the current rising costs of prescription drugs and the precedent that could be set. Instead, each province has been left to its own devices to come up with a solution.

British Columbia is the first province to establish funding formulae. The B.C. Cancer Agency and Ministry of Health set aside $8 million per year for breast cancer patients which began on July 2005 (BC Cancer Agency, 2005). It is expected that about 160 women will benefit from the drug each year. Ontario has followed suit and the Ministry of Health and Long Term Care has provided Herceptin® under a new provincial drug program facilitated by Cancer Care Ontario (Ontario Ministry of Health, 2001). Quebec and Saskatchewan have also been quick to follow, however, other provinces such as Nova Scotia and Prince Edward Island pay for it on a case by case basis.

Some health economics experts are questioning the cost effectiveness of this cancer treatment. As a result, there are international trials which are currently evaluating effectiveness of the treatment in HER2/neu-positive patients with primary breast cancer. Preliminary results are indicating treatment with this drug will lead to high initial cost but if less people progress to metastatic breast cancer, resources can be saved on advanced metastatic treatment which reduces total health cost (Neyt, Albrecht, & Cocquyt, 2005).

Treatment Used	Patients with Cardiotoxicity
Anthracycline and cyclophosphoamide	8%
Anthracycline, cyclophosphoamide, Herceptin®	27%
Paclitaxel and Herceptin®	13%
Paclitaxel	1%

Table 1: Incidence of cardiotoxicity associated with various combinations of therapy for overexpressing HER2/neu MBC patients. Antracycline, adriamycin, cyclophosphoamide, and paclitaxel are all chemotherapeutic agents (Slamon et al., 2001).

Long Term Outlook

As more expensive cancer treatment drugs are introduced, health policy makers and politicians are wondering where to draw the line. Canadians are proud to have a healthcare system that ensures citizens do not pay at the point of access. Legislation such as the Canada Health Act ensure this right is enjoyed across provinces, but if we are to remain faithful to our healthcare roots, the nation needs to act quickly to come up with financing schemes for costly emergent drugs. Robust financing schemes that produce equitable health outcomes are required before we ask ourselves who will be allowed to live. This can only be achieved when there is co-operation between research institutions, biopharmaceuticals, and government agencies.

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