Case Study 4: Trastazumab (Herceptin)

Part 1:

Launched in 1998 by American biotech company Genentech, Trastazumab, better known as Herceptin, is a monoclonal antibody active against the Her-2/neu receptor.

Her-2/neu - or HER2 - is a receptor protein and growth factor, and the gene that codes for it (also called Her-2/neu or HER2, see the OMIM entry for this gene) is present in every cell of the human body. In normal, healthy tissues it is involved in cell growth and division, however in some cancers - frequently breast cancers - it mutates, such that the gene is amplified and these cancer cells contain many more copies than is usual. Where the extra copies of the HER2 gene are expressed (called overexpression), the cancerous cell grow and divide rapidly and uncontrollably. Although HER2 overexpression is associated with a minority of breast cancers (also some ovarian and prostate cancers) so called HER2-positive cancers tend to be the most aggressive and difficult to treat. Metastases are common, not only in breast tissue, but also in lymph, lung and bone. Where such aggressive, metastatic cancer is recurrent the patient's prognosis is generally poor and usually terminal.

Herceptin acts to block the HER2 receptors on the surface of cancer cells, this not only prevents them from growing and dividing quite so rapidly, as it is usually administered with chemotherapy, it allows the cancer cells to be destroyed by chemical means (Animation 1 illustrates this process graphically).

The HER2 status of a tumour can be clinically ascertained in two ways, only one of which involves a genetic level test for HER2 copy number. Initially biopsied material is subjected to an immunohistochemical assay (IHC) and only if the tumour’s HER2 status is ambiguous or borderline is Fluorescence In-Situ Hybridisation (FISH) carried out. These tests classify the tumour into one of four groups according to the level of HER2 (over)expression detected. The groups are termed “0”, “+1”, “+2” and “+3”. The slides below show typical immunohistochemical results for each HER2 status group. The distinction between each of these classifications is made on the basis of intensity of membrane staining¹.

Immunohistochemistry (IHC) slides showing intensity of membrane staining for each HER2 status class.

¹ Slides from Rhodes, A. (2006). “HER2 testing in breast cancer”, The Biomedical Scientist, June, pp.517. See full article for further details, including percentage staining criteria used in classification.
It is the +2 category that is regarded as equivocal and tumour samples scoring +2 are usually submitted for FISH analysis. Here the levels of HER2 gene amplification are assessed in order that Herceptin treatment is targeted at only those patients thought to benefit from it: "If the 2+ case shows gene amplification, the patient is currently presumed to benefit from Herceptin therapy, while a patient with a non-amplified 2+ tumour is thought unlikely to benefit." (Rhodes, 2006: 516)

**Part 2:**

When Herceptin first came onto the market in 1998, it was heralded as a revolution in cancer treatment: it was the first monoclonal antibody to be used successfully in the treatment of cancer and, as a biological rather than chemical treatment, had none of the painful and debilitating side effects associated with aggressive chemotherapy. However, Herceptin's development and clinical testing had been a long and costly process for Genentech (see Bazell, 1998, for further details of this BioethicsBytes post), hence it was initially considered prohibitively expensive for both public and private healthcare providers and patients requiring Herceptin were forced to pay for it themselves. In the UK for example, Herceptin has been licensed as a safe and effective treatment for advanced metastatic breast cancer since 1999, however, it was not until March 2002 that the National Institute for Clinical Excellence (NICE) issued guidance for its provision in these cases on the NHS. Between these dates (i.e. after the drug had been licensed but before NICE has issued guidance) the decision about whether or not to provide Herceptin - at £20,000 per course - on the NHS was left to individual Primary Care Trusts (PCTs). This situation lead to media headlines concerning the Herceptin 'postcode lottery' and stories of neighbouring women who were receiving differential treatment from different PCTs (see for example this article from the BBC News website).

However, the 'postcode lottery' for Herceptin in the interim between the drug's licensing for use in advanced breast cancer and the publication of the NICE guidance was only the first story of Herceptin 'rationing' to hit the UK headlines: for campaigners the battle to gain NHS access to Herceptin for early-stage breast cancer in 2005 was equally daunting. The BioethicsBytes post Herceptin: Wanting the wonder drug describes this episode in detail and highlights the central bioethical question as one of resource allocation within the NHS. While many officials and doctors claimed that Herceptin was withheld from patients with all but the most serious cases of advanced metastatic breast cancer (those where chemotherapy had failed to have any impact on the cancer's progression) because the drug's safety and efficacy were as yet unproven, 

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2 Initially Herceptin was thought to have no side effects at all, but more recently it has been suggested that a particular type of heart condition can be aggravated (possibly even caused) by extended use of Herceptin.


5 Interim results of the BIG/Roche Herceptin Adjuvant (HERA) trials of Herceptin is an adjuvant therapy in early-stage breast cancer only became available in 2005 (see Piccart-Gebhart et al. (2005). "Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer", N Engl J Med., 353(16):1659-72. Available at http://content.nejm.org/cgi/content/full/353/16/1659). However, there remained some queries regarding both the safety and efficacy of this use of Herceptin since a number of participants had withdrawn early due to suspected cardiotoxic side-effects, and Roche terminated the placebo arm of the trial early for ethical reasons (see Boseley, 2006). Full results, including the results of 2 year follow-up studies (which are required in phase III clinical trials which compare the new drugs with existing treatments) were not available.
campaigners and other medical professionals suggested that additional numbers of patients, relative success rates and the cost of Herceptin made it uneconomical for NICE to approve Herceptin for early-stage breast cancer.\(^7\)

In August 2006, following political pressure, NICE approved Herceptin as an adjuvant therapy for women with early stage breast cancer whose tumours express HER2 at a high level.\(^8\) Still, this is a minority of the breast cancer cases that pass through UK oncology clinics. In this sense Herceptin is far from a panacea: for the majority of women whose cancers do not over-express the HER2 protein, Herceptin is ineffective clinically; for the small amount of women whose tumours only over-express the gene weakly (for example those at the lower end of the +2 category) Herceptin - at £20,000 per course - is deemed not cost effective; and, even where Herceptin is effective and the patient's tumours shrink, it is not a cure, since in all but the most exceptional cases, treatment Herceptin and chemotherapy may only add 8-12 months to a patient's predicted life expectancy. Thus, what for many women with breast cancer and their families seems a priceless and invaluable benefit, for others is bought at the expense of patients elsewhere in the NHS. For example, in this episode of BBC Radio 4's The Investigation (first broadcast at 20.00 on November 29 2007), one doctor claims that in 2006 the NHS spent around £100m on Herceptin, though this money only benefited around 500 patients. He believes that if this money were diverted to radiotherapy "it could have a dramatic impact" (for further details see this article on the programme on the BBC News website).

Selected references:


\(^6\) In addition, some coverage of the controversy over access to Herceptin for early-stage breast cancer implies that it parent company, Roche, also had an economic incentive to expand the market for Herceptin. For example, Boseley (2006) states "Herceptin is ... suitable for only 20% of breast cancer patients. Roche, naturally, having spent many millions of pounds on developing the drug, badly wants as big a slice of this restricted market as it can get".

\(^7\) See Orr (2006) for some examples of how NICE calculates cost-benefit for the purposes of drug approval.