BioethicsBytes Extended Commentary

*Her-2: The making of Herceptin, a revolutionary treatment for breast cancer* (Bazell, 1998)

**Introduction to this resource**

Welcome to this *BioethicsBytes Extended Commentary*. These are intended to provide all readers - teachers, learners and members of the public alike – with a more in-depth discussion of issues raised by media presentations of developments in biology and biomedicine. They are supplementary to the posts on the *BioethicsBytes* website, and elaborate themes identified in the main commentaries.

In general, they deal with one or more very specific bioethical issues raised by featured programmes. They focus on specific quotes, or exchanges, in the source material that illustrate moral concerns or ethical concepts that have application beyond the context of the programme. The extended commentaries draw on a wider range of media and academic texts than can be presented on the main website, and, as such, can provide readers with additional resources on specific topics.

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Introduction to Her-2: The making of Herceptin, a revolutionary treatment for breast cancer (Bazell, 1998)

The post that appears on the main BioethicsBytes website deals exclusively with the clinical trials that brought the cancer treatment to market in 1998 (see Her-2: The making of Herceptin, a revolutionary treatment for breast cancer (Bazell, 1998)). This extended commentary attempts to unpack some of the additional bioethical issues that appear in this book.

Herceptin (developed in the US by Genentech, and marketed in the UK by Roche – who, today, own more than 50% of Genentech stock1), is a humanised monoclonal antibody used in the treatment of breast cancer. It is a particularly interesting case as, according to Bazell (1998), it was the first monoclonal antibody to be used successfully in the treatment of cancer, though it is also an example of a pharmacogenetic drug that is only active against a specific sub-group of breast cancers, defined by genetic changes within the cancerous tissue. Specifically, Herceptin is active against “HER2+” cancers that over-express the HER2 (also referred to as Her-2/neu) gene which encodes the growth factor receptor protein. Approximately 20% of breast cancers over express HER2, usually due to amplification of the gene within the tumour, or continuous transcription of existing diploid genes2, and this status is associated with more aggressive progression of the disease.

With respect to this extended commentary, Bazell’s account of the development of Herceptin provides an opportunity to elaborate some of the bioethical issues that may be common to all drug development processes. Thus, although Herceptin is referred to throughout, the issues discussed here have wider significance that this case alone.

The issues covered below are:

- Informed consent for tissue donation in drug discovery;
- Clinical trials as a social and emotional affair;
- Balancing the needs of the many and the needs of the few;
- Why is Herceptin a ‘wonder drug’?

1. Informed consent for tissue donation

The first of these additional bioethical issues raised by Bazell’s book concerns research ethics in drug discovery, specifically the use of "tissue collections", which in this case were composed of tumour samples donated by patients. Interest in research ethics is apparently increasing and an appreciation of the issues involved is now required by several AS and A2 biology curricula in the UK (see the BioethicsBytes "Bioethical content within the new AS and A2 Level Biology specifications" website for further details).

In the first five chapters, of Bazell gives an account of the scientific research that contributed to the initial development of Herceptin. One of the most significant scientists (and later advocates) for this research was Dennis Salmon, then a faculty member in the

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Department of Haematology-Oncology at UCLA in California. While Bazell eloquently describes Salmon's dedication to "the pursuit of a cure" (Bazell, 1998: 37), he also notes how this involved what Bazell terms "a bizarre hobby" (1998: 37). Bazell states: "he [Salmon] collected freshly excised human tumours - lung, liver, breast, colon, whatever he could get from surgeons and pathologists" (1998: 37). This included a "collection of thirty breast cancer tumours" (1998: 39): a collection which played a role in the discovery of the Her-2/neu gene's connection to breast cancer (Her-2/neu is now simply known as HER2, see OMIM entry). While the consenting of this tissue is not explicitly stated in Bazell's book (either for the use of tissue in 'basic research' or retention and storage), he does date its use in the discovery of Herceptin back to 1986 - arguably a time before consent for tissue retention of any kind became a social, legal, political, ethical and scientific issue (in the UK, scandals at the Alder Hey hospital in Liverpool and at the Bristol Royal Infirmary brought the issue to widespread public attention in the early 1990s, and ultimately led to the Human Tissue Act 2004 - see Alder Hey Scandal for example).

While Bazell gives us no reason to believe the tissue donation and retention was not consented, reflection upon this case and the subsequent role of those tissues in the discovery of a "revolutionary" new treatment for breast cancer raises a number of interesting questions for debate: If this tissue was not consented, was its retention and use in drug discovery research ethical practice? Does it make a difference if that unconsented tissue goes on to form a part of the process which goes on to save a number of lives (as the licensing of Herceptin arguably has)? Is retrospective consent a viable ethical alternative? Would Salmon's patients have consented at the time - that is if we deem it possible and/or ethical to ask patients in a highly distressed state and situation to read, comprehend and hence be 'informed' about the tissue retention process (it is likely Salmon's collection was composed of initial biopsy samples, since these are the most valuable in cancer research as they are uncontaminated by chemical, radiation or antibody treatment)?

2. Clinical trials as a social and emotional affair

One of the strengths of the *Her-2* book is that it explores the process of trialling a new drug from both the clinical and social point of view. An important aspect of this is the way that the small phase I and phase II trial groups formed close knit social ties centred around their treatment experience. This enabled the participants to share support, information and resources, and - according to Bazell - to form friendships that lasted throughout the trials and beyond.

During phase I and phase II trials of Herceptin (in accordance with the protocol approved by the FDA) the participants were given eleven transfusions of the antibody (in the case of the UCLA phase I patients, in combination with cisplatin). These were administered intravenously on a weekly basis in the 'infusion room'. In the case of Salmon's phase I group, participants received infusions together, a procedure that was thought to have facilitated the formation of strong ties between them. While Bazell does not suggest that this group cohesion was viewed entirely negatively, by either clinicians or company, he does seem to suggest that the bonds between the women made the highs of Herceptin's early success exhilarating, though also, made the inevitable phase I deaths even more difficult to accept. Thus, following the experience with Salmon's group "doctors decided that in future patients would be treated individually" (1998: 85), as was the case with the phase II trial group at Sloan Kettering. However, this group also seemed to form strong
bonds, and in this case their contacts extended beyond the treatment group into the wider community of breast cancer activists. In this case, the way the trial group bonded apparently played a role in, not only, providing women in a desperate situation with a support system and social network, but also, the campaign for compassionate access to the experimental Her-2/neu antibody in the early 1990s (see particularly pages 116-117).

3. Balancing the needs of the many and the needs of the few

Balancing the best interests of a population of patients – the many - with those of individuals – the few - is a classical problem in biomedical ethics. It manifests itself in a number of forms, and can create difficult ethical dilemmas for those in positions of authority (consider, for example, mass vaccination, and in particular questions concerning the MMR vaccine in the 1990s – see BioethicsBytes post MMR: our children, our choice? - Panorama). In the case of Herceptin there is an apparent tension between Genentech’s obligations – as a manufacturer of therapeutic drugs – toward individual breast cancer patients (with whom they and their clinical staff/representatives have personal contact), and the wider community of current, and future, breast cancer sufferers. In terms of the Her-2/neu antibody trials this is represented in (at least) two ways:

1. **Negotiations over “compassionate access” to Herceptin.** Bazell (1998) provides a detailed account of how and in what form breast cancer activists gained access to Herceptin before it had been licensed on compassionate grounds (notably pages 113-123 and 125-131). However the need to balance the needs of a few patients who wanted – and from their point of view, desperately needed – Herceptin right away, and those of a wider population who would benefit most from the speedy licensing of the drug, is summarised in Genentech’s rationale for not providing compassionate access to the drug: “Giving an experimental drug to a few people before it was proved effective wasted resources, time, and money that should be spent on either proving whether this drug works or searching for other drugs that might” (Bazell, 1998: 117-118).

2. **The design of and reporting of phase III clinical trials:**

   • **The placebo-controlled protocol.** Several of the problems associated with Genentech’s initial use of a double-blind placebo controlled design for the phase III trials are discussed in the main HER-2 BioethicsBytes post, and although this protocol was eventually revised, its continuation would have raised an interesting question. As the ‘gold standard’ in clinical trial design, this protocol would arguably have eased the path to Herceptin’s licensing and, therefore, its use in a wider population. However, insofar as it was a key barrier to trial recruitment, it threatened to lengthen the time to completion of this final phase of testing (see Bazell, 1998: 159). Thus, in deciding whether or not to drop the placebo, Genentech were effectively balancing the needs of the many women who would benefit from Herceptin’s ultimate licensing and those who might die should the study design delay this process.

   • **Could Herceptin have been licensed on the basis of results from the 649 trial alone?** On page 166, Bazell describes Salmon’s desire to submit a license application for Herceptin to the FDA on the basis of results from the 649 trial
alone which would have been available earlier than those for other parts of
the phase III trials. However, as the 649 participants were patients with
advanced metastatic disease, any license obtained would reflect this study
group. The question here is that, if Herceptin had been licensed earlier though
for use only in advanced cases, could a small number of lives have been
saved? As opposed to waiting until the results from the early stage trial
groups were in and being able to provide Herceptin to a much larger patient
population at a later date?

In all these cases Genentech were effectively balancing the needs of a small number of
women with those of a potential though larger patient population. This consequentialist
calculus is likely to be implicit for all pharmaceutical companies engaged in clinical trials,
and Genentech faced and made all three choices in the course of Herceptin’s testing.

4. Why is Herceptin a ‘wonder drug’?

The final additional bioethical issue raised by Bazell is more of a puzzle than dilemma. In
reporting the results of the phase II trials of Herceptin (alone and in combination with
cisplatin) – which are summarised below, in Table 1 – he notes that: “The results of the
Her-2/neu phase II trial would discourage any medical researcher except an oncologist. An
antibiotic that cured one in forty-three infections would be deemed a failure” (1998: 106).³

<table>
<thead>
<tr>
<th>Objective response</th>
<th>Herceptin alone (n=43)¹</th>
<th>Herceptin/cisplatin combination (n=37)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor response OR Stable disease</td>
<td>16 37.2%</td>
<td>9 24.3%</td>
</tr>
<tr>
<td>Disease progression</td>
<td>22 51.2%</td>
<td>19 51.3%</td>
</tr>
</tbody>
</table>

¹ Baselga et al. (1996).
² Pegram et al. (1998).

Table 1: Results from Phase II trials of Her-2/neu antibody

This raises the following question: what is so special about Herceptin and/or the condition
it treats that it should be hailed a ‘wonder drug’ when, in other areas of medicine,
experimental drugs with similar phase II (i.e. efficacy) results would be deemed failures?
There are a number of answers to this question – some obvious and some less so –
however, the ethical issue here is one of parity, or at least comparability, between notions
of ‘successful treatment’ in different areas of medicine. Where ‘success’ is defined

³ In Table 1, the category ‘objective response’ includes both complete and partial remission (n=1 and n=10,
respectively). The “one in forty-three” that was cured referred to in this quote from Bazell, denotes the one
patient within the Her-2/neu antibody alone trial group that achieved a complete remission.
differentially across medical specialities, this could raise questions about the prioritisation – both academically and commercially - of those areas where 'success' may be relatively easier to achieve.

References

