Trastuzumab: possible publication bias
Scott Metcalfe, Carl Burgess, George Laking, Jackie Evans, Susan Wells, Steffan Crausaz
The Lancet, 17 May 2008

Herceptin (trastuzumab) for early breast cancer has caught international attention. Yet its effectiveness may be overestimated, because important clinical trial data from nearly 1000 women have not been published.

Publication bias is of increasing concern, entrenching the use of inferior treatments. This concern now extends to adjuvant trastuzumab (Herceptin) in women with HER2-positive early breast cancer, because a key clinical trial has been only selectively published. As such, patients are being given an important treatment sequence that may be much less effective than currently thought.

Adjuvant trastuzumab can be given in two main sequences: concurrently with or sequentially after other chemotherapy. Sequential treatment is licensed, is standard practice and is the publicly funded regimen in many countries, such as most of Europe (United Kingdom included). One randomised trial (out of six relevant trials), by the North Central Cancer Treatment Group (NCCTG), trial NCCTG-N9831, has studied both sequential and concurrent treatments head-to-head, together with a control or usual-care group. However, although this three-group study has important implications for how best to use trastuzumab, it has only been partly published. Data from the 985 women given 12-month sequential trastuzumab in this study are in effect missing, despite publication of data from the 12-month concurrent and control groups of the same trial nearly 3 years ago.

Interim results for all three groups of the NCCTG trial were presented orally in 2005 the American Society of Clinical Oncology annual meeting. After 1.5 years’ median follow-up, sequential trastuzumab gave a comparatively small 13% relative reduction in disease events compared with usual care—with a reasonable chance of being no better than the control arm (hazard ratio 0.87, 95% CI 0.67–1.13). Conversely, concurrent trastuzumab was significantly more effective than sequential therapy, reducing disease events by a third (0.64, 0.46–0.91).

Soon after, Romond and colleagues published the concurrent and control group results from the NCCTG three-group study with another study of concurrent treatment (the National Surgical Adjuvant Breast and Bowel Project [NSABP] B31 trial) in a retrospectively approved pooled analysis. Limited efficacy data from the individual trials are available in the online appendix to that publication, but do not include the NCCTG sequential-group data. These data are only available as part of a slide presentation on a conference website, and have never been disseminated by peer-reviewed publication.

The selective release of data from the NCCTG study has far-reaching implications for women with HER2-positive early breast cancer. Without these data, sequential trastuzumab seems more effective than it probably is. Combining the NCCTG sequential data from the conference slide show with updated results for the other trials of sequential trastuzumab (HERA and PACS-04) shows a treatment effect one-third less than initially estimated (HERA 12-month median follow-up, 0.54, 0.43-0.67 vs HERA 23-month median follow-up, 0.72, 0.67-0.78; 18% absolute difference) —see Figure One below. More events will have accrued since 2005, which will further affect pooled estimates.
We understand that although the updated combined analysis for the concurrent group in the NCCTG study and NSABP-B31 will soon be published, the NCCTG study’s sequential group data will be presented and published only when the number of events is believed sufficient to ensure analysis has the appropriate statistical power.

However, the same criteria for analysing both efficacy and adverse effects should apply to both the sequential and concurrent groups of the NCCTG study. For the NCCTG and NSABP studies, the proper approach would be to publish all efficacy data from both trials separately (enabling assessment of between-trial variability), as has been done for cardiotoxicity. Instead, what has been published and presented is post-hoc pooled analyses limited to concurrent treatment groups that were of appreciably different design.

The NCCTG three-group study had enough power to detect a statistically significant difference between its concurrent and sequential treatments. But even when trials are underpowered, their data should still be published to inform meta-analysis. Interestingly, the positive results from the NCCTG study’s concurrent group were released despite reaching less than half of the prespecified event count required for first interim analysis (140 events occurring vs 331 events required; 663 events were required for final analysis, so 331 is the 50% of events prespecified for the planned first interim analysis). Furthermore, toxicity data from all three NCCTG groups have been considered mature enough to publish, the sequential arm included.

Comments in trial reports and reviews consider the NCCTG sequential-group data to be relevant and important. The 3-year follow-up data have already been presented for the NCCTG concurrent and usual-care groups (see Figure Two below), so are likely to also be available for the sequential group.

Failing to publish inconclusive results can mean wide (and wasteful) use of ineffective treatments, or even unnecessary illness and death if the reported risks of harms are underestimated. Clearly adjuvant trastuzumab is effective, but how best to use it appears to have been hampered by some publication choices that presently are unclear.

There is a duty of care to trial participants, sponsors, regulators, and the public good to promptly publish outcomes in all exposure groups. This topic is notably underplayed in current statements on good clinical practice for reporting, and also in official directives on the conduct of trials.

Is it now time the efficacy data from the entire NCCTG study, with updated events accrued since 2005, see the light of day?

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Conflicts
PHARMAC (SM, JE, SC) is funding a concurrent 9-week regimen of trastuzumab for HER2-positive early breast cancer in New Zealand. CB chairs the Pharmacology and Therapeutics Advisory Committee to PHARMAC. GL has provided legal expert testimony for PHARMAC about trastuzumab. SW has provided external critical appraisals, commissioned by PHARMAC, of the trials of adjuvant trastuzumab.

Acknowledgements
We thank Prof. Klim McPherson, Prof. Curt Furberg, Dr. Daniel Hind, Prof. Chris McCabe, Dr. Richard Richards, Prof. Anthony Rodgers, Prof. James Wright, Prof. Sir lain Chalmers, Prof. Richard Beasley, Dr. Jonathon Howell, Dr. Daphne Austin, and Dr. Jane Wells.

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Figures

Figure One. Efficacy of sequential 12-month trastuzumab in HER2-positive early breast cancer:

![Graph showing hazard ratio for disease recurrence events](image)

Contributing data:

<table>
<thead>
<tr>
<th>Trial where adjuvant trastuzumab given sequential to other chemotherapy</th>
<th>H/Adm N vs. cntrl N</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA 12-month f/up</td>
<td>127/1694 vs. 220/1693</td>
<td>0.54 (0.43-0.67)</td>
</tr>
<tr>
<td>HERA 23-month f/up</td>
<td>218/1703 vs. 321/1698</td>
<td>0.64 (0.54-0.76)</td>
</tr>
<tr>
<td>NCCTG-N9831 Arm B (sequential)</td>
<td>103/985 vs. 117/979</td>
<td>0.87 (0.67-1.13)</td>
</tr>
<tr>
<td>PACS-04</td>
<td>59/260 vs. 70/268</td>
<td>0.86 (0.61-1.22)</td>
</tr>
<tr>
<td>Pooled HERA 23-month f/up / N9831 Arm B (sequential) / PACS-04</td>
<td>380/2948 vs. 508/2945</td>
<td>0.72 (0.67-0.78)</td>
</tr>
</tbody>
</table>
Figure Two. Time course of the RCTs reporting efficacy outcomes for adjuvant trastuzumab in HER2-positive early breast cancer

Five of the six trials reporting disease outcomes with adjuvant trastuzumab compared with standard chemotherapy treatment in HER2-positive early breast cancer (HERA, NCCTG-N9831, NSABP-B31, FinHer, BCIRG006) have reported interim efficacy results, but have varied by the timing of patient accruals, when results were initially reported, and when (if) published. PACS-04 has reported final results for its HER2-positive patients, having met its preset target event accruals; these remain unpublished.

Results from 5-year median follow-ups (some being final analyses) should be available between mid 2008 and late 2009.

Key:
[i] crossover of patients from standard care arm to trastuzumab arms (HERA), or crossover from standard care or sequential trastuzumab arms to concurrent trastuzumab arm (N9831)
[ii] interim efficacy analysis
[iii] data lock – date that database closed and the data were locked for analysis
[iv] reported – date that results first presented at conference or reported in lay media
[v] published – date that results from the individual trial first published in peer reviewed journal

A seventh study, ECOG E2198, which compared 12 months with 10 weeks trastuzumab given concurrently with paclitaxel, was presented as a poster at the San Antonio Breast Cancer Symposium in 2006 (Sledge et al, http://www.abstracts2view.com/sabcs06/view.php?nu=SABCS06L_561). However, this was a pilot study not designed to test efficacy nor powered to determine equivalence and has not reported outcomes against standard chemotherapy treatment.
1. Publication bias emerges when the published trials do not represent all the trials undertaken for a particular intervention, usually because statistically significant results tend to be submitted and published more frequently than indeterminate results. Recent examples include trials relating to celecoxib and paroxetine.

2. Trastuzumab (Herceptin) was discovered and developed by Genentech, a U.S. biotechnology company in which Roche holds a 67 percent stake. In July 1998, Genentech granted Roche exclusive marketing rights for Herceptin outside the United States.

3. A number of countries have licensed a sequential 12-month trastuzumab treatment regimen. There appears to be a division between the USA and the rest of the world for sequencing (sequential vs. concurrent), according to which company markets trastuzumab.

4. Six RCTs have reported disease outcomes for adjuvant trastuzumab compared with standard chemotherapy treatment alone in HER2-positive early breast cancer. Trastuzumab started concurrently with paclitaxel (n=979). Doxorubicin/cyclophosphamide (AC) followed by 12 months trastuzumab sequential to (after) chemotherapy arm (Arm B) used AC-T followed by 12 months trastuzumab given sequentially to paclitaxel (n=985). The trastuzumab given concurrently with chemotherapy arm (Arm C) used doxorubicin/cyclophosphamide (AC) followed by 12 months trastuzumab started concurrently with paclitaxel (n=979).

5. Interim results have known risks of overstating true treatment effects, as has also occurred elsewhere with adjuvant trastuzumab (e.g. in the HERA trial). Analysis of NCCTG-N9831 only on specialist conference websites (including Europe and Canada) gaining licensing for sequential treatment includes the United Kingdom.

6. NCCTG-N9831’s usual care chemotherapy arm (Arm A) treated patients with doxorubicin/cyclophosphamide, followed by paclitaxel, AC-T (n=1162 patients). The trastuzumab sequential to (after) chemotherapy arm (Arm B) used AC-T followed by 12 months trastuzumab given sequentially to paclitaxel (n=985). The trastuzumab given concurrently with chemotherapy arm (Arm C) used doxorubicin/cyclophosphamide (AC) followed by 12 months trastuzumab started concurrently with paclitaxel (n=979).

7. ‘Disease events’ in this Comment derive from disease-free survival (DFS) in all six RCTs that have reported outcomes for adjuvant trastuzumab in HER2-positive early breast cancer studies. DFS incorporates both recurrence of breast cancer and death without recurrence.

8. The NCCTG-N9831 study has informally reported the outcomes for 965 women treated with trastuzumab sequentially. The failure to show significant improvements in DFS with sequential treatment (Arm B) compared with standard care (Arm A) may not be simply due to the play of chance, with fewer events and patients for analysis. It may actually show a lower efficacy of the sequential approach (with the hazard ratio being only 0.87 on interim analysis).

9. The N9831 and B31 trials of concurrent regimens in the Romond 2005 interim analysis differed in patient eligibility (high risk negative node status); methods of randomisation allocation; taxane regimens, anthracycline regimens, sequencing with radiotherapy, sequencing with hormonal therapy, aromatase inhibitor types, and when they were started to be used in the trials; recommendations for post surgical radiotherapy; and primary endpoints (disease-free survival (DFS) for N9831, overall survival for B31).

10. The posting of these important results for the sequential arm of NCCTG-N9831 only on specialist conference websites makes them unlocatable on Medline searches etc. and they are not subject to peer review and other scrutiny.

11. The non-publication of Arm B has extended to information about cross-over of patients from the control arm and taxane chemotherapy.
sequential arms (A, B) not being available on public record – which may be important for the interpretation of ongoing publications of Arm C results. The N9831 data monitoring committee was sufficiently impressed by the interim results of the N9831 trial to offer subjects not only in Arm A (control) but also B (sequential) the opportunity to have concurrent trastuzumab (i.e. crossover to Arm C) – in its view an ethical decision based on the results it viewed. Arm A patients could switch to trastuzumab (arms B or C) from April 2004, and Arm B patients could switch to concurrent trastuzumab (Arm C) from January 2005 [letter from RocheNZ to PHARMAC dated 6 March 2007].

12. Concerns around whether NCCTG-N9831 was sufficiently powered prospectively to assess sequential treatment can be allayed by the trial’s results as reported, albeit unpublished. The statistically significant result presented at ASCO 2005 for the concurrent versus sequential arms (HR 0.64, 95% CI 0.46-0.91)\(^2\) means that it emerged that the study was indeed sufficiently powered to detect this difference. This is where once results become available then the power of the trial is expressed in its treatment effect’s confidence interval, rendering prospective power considerations to be obsolete.\(^3\) The 0.46-0.91 confidence interval for the DFS hazard ratio comparing N9831’s concurrent arm with its sequential arm (stratified logrank 2p value 0.0114) was derived from just 23% (n=137) of the 590 pooled events in these two arms that the prospective power calculations had predetermined to be necessary.\(^4\)

13. As noted in the NCCTG-N9831 ASCO conference presentation\(^2\), during patient accrual, at any time patients in Arm C (concurrent) would have received three additional months of trastuzumab compared with patients in Arm B (sequential). This difference in the phasing of exposure to trastuzumab treatment has the potential to understate both the efficacy and adverse effects of sequential treatment compared with concurrent treatment. Presumably this issue will have been recognised and accounted for in pre-planned trial protocol for statistical analysis, and would be at least be discussed in a formal peer-reviewed publication of the results.

14. The NCCTG-N9831 Arm B vs. A events were analysed at around April 2005, compared with May 2006\(^12\) for the 23-month median follow-up for HERA trial. Had the N9831 Arm B vs. Arm A results been re-analysed and then presented at the same time as were HERA 23-month median follow-up data at the 2006 ASCO conference, the additional numbers of events could appreciably influence the weight given to N9831 Arm B in estimates of overall efficacy of sequential trastuzumab.

However, this needs to be balanced against attrition bias, where the inclusion of patients pre-surgery and radiotherapy in N9831 means that numbers of treatment failures (in all arms) are proportionately greater than in HERA (patients in HERA were enrolled following the completion of surgery and radiotherapy).

15. Publishing all data from each of the arms of the NCCTG-N9831 and NSABP-B31 trials separately would also enable assessment of between-trial variability. Identifying variation in response between patient groups/study designs is important for systematic reviews.
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