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Crossover in Adjuvant Trastuzumab Trials
Sparing Toxicity in Patient Care

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Objectives: Design and reporting of randomized control trials for drug therapies in the adjuvant setting require a nuanced consideration of patient crossover. Adjuvant trials can be susceptible to the misuse of crossover and may distort the interpretation of findings. We sought to investigate and describe crossover and/or postprogression access to trastuzumab within adjuvant trastuzumab randomized control trials for human epidermal growth factor receptor 2–positive breast cancer patients.

Methods: Seven clinical trials for adjuvant trastuzumab in human epidermal growth factor receptor 2–positive breast cancer were identified through a meta-analysis published in the *Lancet*. Primary study publications were located through MEDLINE, Google Scholar, and trials were identified, when possible, using Clincialtrials.gov.

Results: Sixteen publications, describing 7 studies, were reviewed. Four (57%) trials reported offering patients within the control arm the opportunity to crossover and receive trastuzumab in the adjuvant setting. Two (29%) trials did not report nor discuss crossover within the publication. Five (71%) trials reported the total number of patients who crossed over among the control arms. No trials specified the proportion of control patients who received trastuzumab at recurrence.

Conclusions: Trials for adjuvant trastuzumab did not disambiguate between crossover (1) in the adjuvant setting or (2) at recurrence. Due to the low reported rate of crossover, it is questionable if participants received the standard of care.

Key Words: oncology, trastuzumab, trial design

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Trastuzumab (Herceptin; Genentech, South San Francisco, CA) is a transformational drug for women with human epidermal growth factor receptor 2 (HER2-positive) breast cancer. The antibody was initially approved by the US Food and Drug Administration (FDA) in 1998 in metastatic breast cancer patients after a randomized control trial (RCT) demonstrated an overall survival benefit in combination with chemotherapy as compared with chemotherapy alone.[1] In the years that followed, the drug showed benefit in combination with other chemotherapy regimens in the metastatic setting and was eventually tested to determine its role in the adjuvant setting.[1,2]

Between 2000 and 2005, 7 adjuvant randomized trials of trastuzumab were attempted to assess the efficacy of trastuzumab when used after surgical removal of a primary, locoregional cancer.[3] Improvements in disease-free survival (DFS) as compared with placebo led the FDA to approve trastuzumab in this setting in 2006.[1] A recent meta-analysis utilizing direct patient data from published RCTs confirmed the efficacy of trastuzumab as an adjuvant treatment in early-stage HER2-positive breast cancer patients in terms of reducing recurrence and breast cancer mortality and overall mortality[3]

When drugs that have been validated in the metastatic setting are tested in the adjuvant setting, it is important to provide control arm participants access to the drug in the event they develop metastatic disease.[4] For example, by 2005, women randomized to the control arm of adjuvant trastuzumab trials should receive trastuzumab in the event they progress since it had been established as the standard of care for 7 years. If trastuzumab was not provided to control arm patients when they relapse, interpretation of claims of survival benefit in the adjuvant trial become uncertain. The trial essentially tests a strategy of adjuvant therapy against therapy upon relapse that is inferior to the current standard of care.

When trials testing adjuvant drugs are halted by the Data and Safety Monitoring Board (DSMB) for efficacy on the primary endpoint of DFS, it is typical that sponsors crossover remaining patients assigned from the control arm to the active therapy arm out of respect for the participating person.

Thus, in randomized trials of trastuzumab, there may be 2 ways control arm patients go on to receive trastuzumab: either in the event they have relapse or in the event the trial is halted for efficacy. Here, we sought to investigate and describe crossover and/or postprogression access to trastuzumab within adjuvant trastuzumab RCTs. Specifically, we were interested in disambiguating between 2 types of crossover: (1) crossover which occurs within the adjuvant period of treatment, (2) crossover (or post-progression) which occurs at recurrence.

METHODS

Study Selection

We drew upon a recent meta-analysis of randomized trials of trastuzumab in the adjuvant setting published in the *Lancet Oncology*.[3] Seven clinical trials for adjuvant trastuzumab in HER2-positive breast cancer were identified.[3] Primary study publications were located through MEDLINE, Google Scholar, and trials were identified, when possible, using Clincialtrials.

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gov. Records were screened, retrieved, and assessed for eligibility in accordance with the PRISMA diagram (Fig. 1).[5]

Data Extraction

Using primary study publications, we extracted the following data: years of enrollment, country(s) of participating sites, control arm sample size, patients with recurrence, and trial design factors. Recurrence rate of patients in the control arm were extracted from Bradley and colleagues meta-analysis since it was the most recent publication. All data was publicly available and did not include patient-identifiable information, thus in accordance with 45 CFR §46.102(f), institutional review board approval was not required.

Classification of Trials

Trial design was categorized into variables as followed: (1) allowance of crossover in trial design, (2) total number of intent-to-treat (ITT) control patients who received trastuzumab, (3) subgroup of ITT control patients who received trastuzumab in the adjuvant, (4) subgroup of ITT control patients who received trastuzumab after recurrence.

Statistical Analysis

Descriptive statistics were performed and reported throughout.

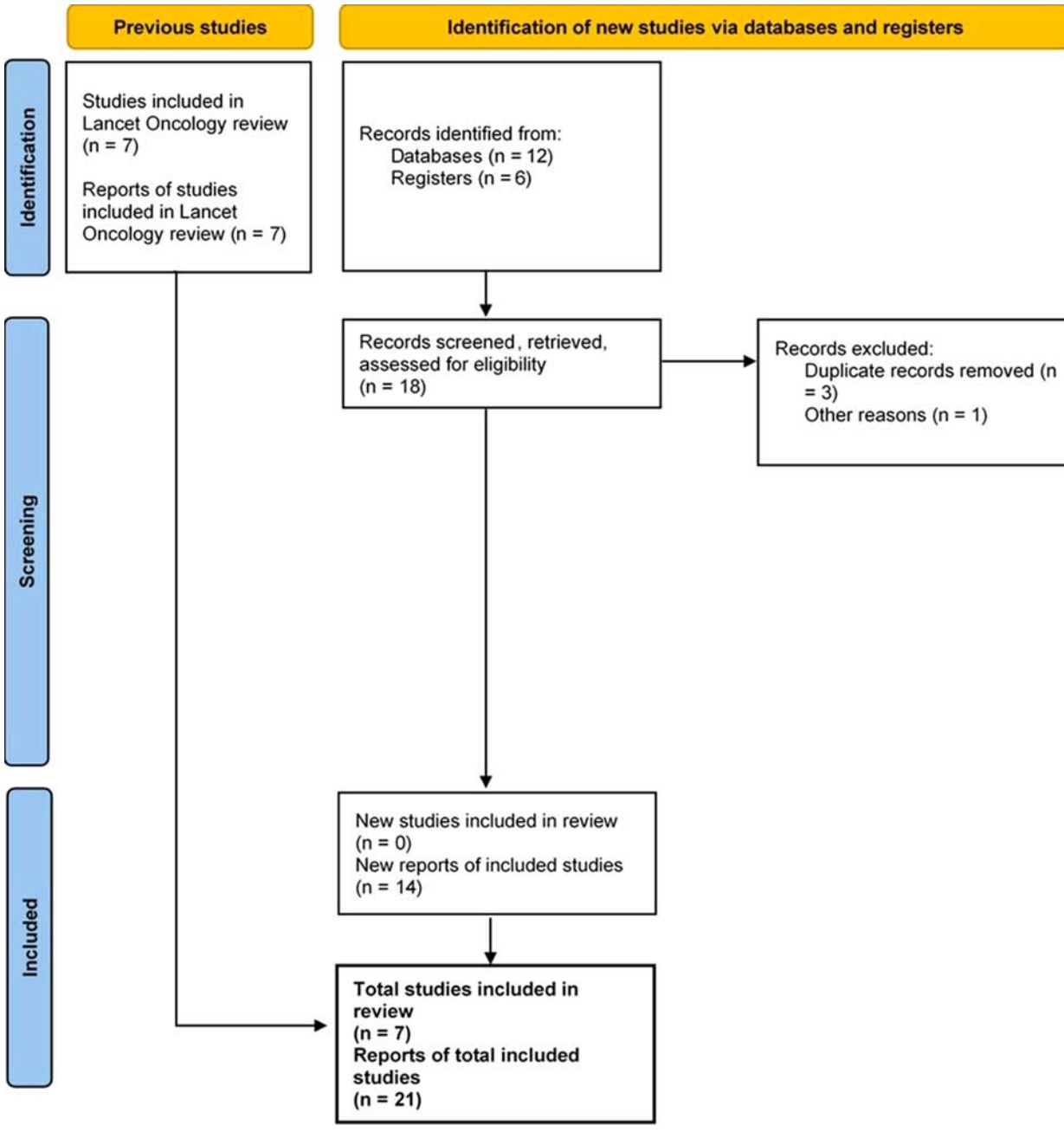

FIGURE 1. PRISMA diagram of systematic search 5. full color online

TABLE 1. Characteristics of Adjuvant Trastuzumab Clinical Trials

	FinHER[3,6,7]	NSABP[3,8–10]	NCCTG Trial N9831[3,8,9,11]	HERA[3,12,13]	PACS 04[3,14,15]	BCIRG 006 Trial[3,16]	NOAH[3,17,18]
Years of enrollment	2000-2003	2000-05	2000-2005	2001-2005	2001-2004	2001-2004	2002-2005
Control arm (n)	116	1061	1232	1697	268	1073	118
Recurrence in control, n (%)	39 (34)	351 (33)	347 (28)	563 (33)	96 (36)	261 (24)	62 (53)
Reported allowed crossover	NR	Yes	Yes	Yes	NR	NR	Yes
Crossover from control to trastuzumab (n)	NR	382	225	884	NR	33	19
Percent of control crossover	NR	36%	18%	52%	0%	3%	16%

NR indicates not reported.

RESULTS

Of the 7 trials under study, we reviewed 16 publications and found 4 (57%) trials reported offering patients within the control arm the opportunity to crossover and receive trastuzumab in the adjuvant setting (Table 1). Two (29%) trials did not report nor discuss crossover within the publication. Five (71%) trials reported the total number of patients who crossed over among the control arms. No trials specified the proportion of control patients who received trastuzumab at recurrence. No trials disambiguated whether crossover was performed due to relapse or a halted study.

The median duration of follow-up was 10.5 years. The chemotherapy backbones that trastuzumab was paired with include: docetaxel, vinorelbine, doxorubicin+cyclophosphamide+paclitaxel (AC-T), Previous (neo)adjuvant anthracycline-based chemotherapy, fluorouracil+epirubicin+cyclophosphamide (FEC), epirubicin+docetaxel (ED), doxorubicin+cyclophosphamide+docetaxel, docetaxel+carboplatin, or paclitaxel+doxorubicin followed +cyclophosphamide+methotrexate+fluorouracil.

In these 7 trials, the percent of women in the control arm who experienced a DFS event ranged from 24% to 53%, with a median of 33% (31% to 35%). The percentage of patients in the control arm that received trastuzumab, when reported, ranged from 0% to 52%, with a median of 17% (interquartile range: 6% to 32%).

DISCUSSION

When 7 adjuvant randomized trials of trastuzumab were launched, the standard of care for women with relapsed or de novo metastatic HER2-positive breast cancer required the addition of trastuzumab. Thus, among the fraction of patients who relapsed in the control arm (which ranged from ~24% to 53%) should have received access to trastuzumab. This is critical for interpretation of endpoints beyond DFS, such as overall survival. For example, the relevant question in adjuvant trials of trastuzumab is not: is receiving trastuzumab after surgery better than never receiving trastuzumab. Rather the question is: does receiving trastuzumab after surgery provide superior benefit (in respect to survival or quality of life) than giving trastuzumab to only the women who relapse. Because adjuvant therapies inherently add toxicity and lengthen the duration of treatment, women who otherwise would not be treated or who could be treated with fewer drugs are thus subject to increased toxicity and reduced health-related quality of life. Whether this is offset by gains in increasing curative fraction or prolonging survival is the relevant medical and scientific question.

Our findings suggest ambiguity in reporting crossover and/or postprogression access to trastuzumab within adjuvant trials of trastuzumab in HER2-positive breast cancer patients. Our findings suggest a poor access to trastuzumab at relapse or progression, that was considered a standard of care before the starting enrollment in these trials.

Among the 7 clinical trials of trastuzumab in the adjuvant setting, 4 (57%) reported allowing control patients access to adjuvant trastuzumab but did not disambiguate the relative proportion of crossover occurring during the adjuvant setting or at recurrence. Of the 5 (71%) trials reporting the number of patients who switched to the experimental arm, all used the terminology "crossover." No report listed postprotocol access to trastuzumab.

Within these trials, trastuzumab could be received by patients in the control group in 2 different situations. First, crossover within the adjuvant setting, meaning that the patient still in the control arm but during the adjuvant setting would receive trastuzumab. The second situation is crossover (or postprogression) trastuzumab at recurrence, meaning that a patient would receive trastuzumab only when a progression occurs. Given that trastuzumab was already known to be beneficial for metastatic patients, this treatment should have been provided for every patient (100%) relapsing within adjuvant trials, regardless of the allocated arm.

Indeed, this is very unlikely that patients had free access to trastuzumab at recurrence in these trials. Within the HERA trial, the trial reporting the highest rate of crossover, we illustrate the range of possibilities for the proportion of patients receiving trastuzumab at relapse (Fig. 2). If all crossover patients received trastuzumab during the adjuvant setting, that means that 0% of them received it at relapse (Scenario A). At the other extreme (Scenario B), all crossover patients (54%) received trastuzumab at recurrence, but this is still low as compared with the standard of care, that should be 100%.

While some trials reported allowing crossover in the adjuvant setting, we showed that they did not disclose the number of patients who received it at recurrence. This can be misleading for readers that could inaccurately think that patients at relapse had fair access to the standard of care. Crossover in oncology RCTs is a concept that is not always easy to understand. Authors from our group advocated for better use of crossover across trial designs.[4]

Limitations

There are 2 limitations to our study. First, all data was extracted from published reports, and thus we are limited by the disclosure of authors. Second, all trials enrolled in 2000 to 2005. Postprotocol standards have evolved in the 15 years since the start of the studies. Whereas underreporting was more common in the past, today's trials often have more robust reporting.

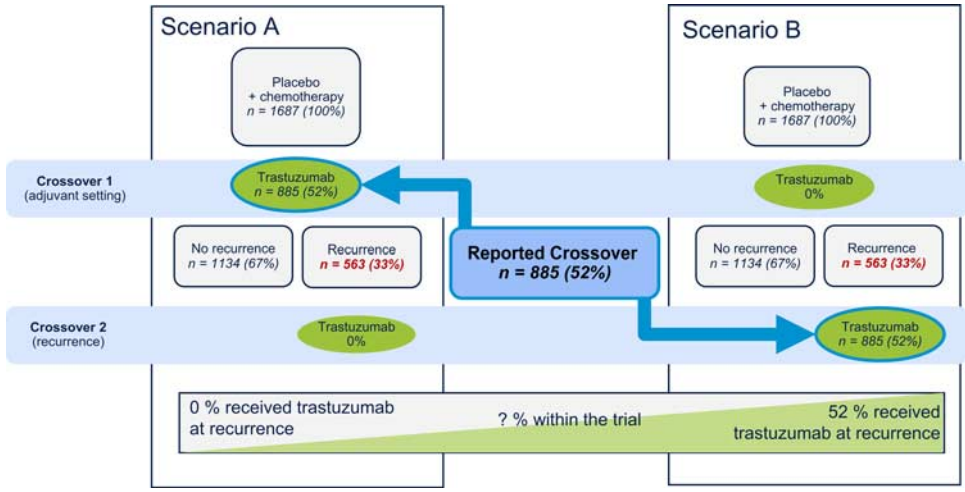

FIGURE 2. Diagram of the two types of crossover: (1) in the adjuvant setting, (2) at relapse. Within the trial with the highest rate of reported crossover (HERA trial), we illustrate the range of possibilities for the proportion of patients receiving trastuzumab at relapse. Panel A: all patients received crossover during the adjuvant setting. Panel B: all patients received cross-over at recurrence. In both scenarios, patients receiving trastuzumab at relapse remain low as compared with standard of care that should be 100%. full color online

CONCLUSIONS

Trials investigating moving a drug like from a latter line to an earlier setting, or even earlier in the adjuvant setting, should be transparent regarding the access to standard of care for patients relapsing. Drugs which already have a proven clinical benefit in latter lines must be provided at progression, either as protocol crossover or outside the protocol.[4] This is the only way to answer the true question: is it beneficial to treat patients earlier? In the adjuvant setting, where a proportion of patients are already cured, the question is even more accurate: can we spare the toxicity (physical, financial, and time) to the fraction of patients that won't recur?

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