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COMMENTS AND CONTROVERSIES

Choosing the Best Trastuzumab-Based Adjuvant Chemotherapy Regimen: Should We Abandon Anthracyclines?

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The identification and effective targeting of the human epidermal growth factor receptor 2 (HER2) and subsequent development of the anti-HER2 antibody trastuzumab redefined our approach to breast cancer and raised hopes that targeted therapies could effectively treat this tumor subtype with less or even no chemotherapy. In the metastatic setting, we have learned that anti-HER2 agents add to the effectiveness of chemotherapy, that the specific chemotherapy partner is of little importance in determining the effectiveness of the regimen, that multiple lines of anti-HER2 treatment are effective, and that the addition of novel antibodies or the use of novel antibody–chemotherapy conjugates may yield better outcomes than seen with conventional chemotherapy and concurrent trastuzumab alone.

For patients with curable, early-stage, HER2-positive breast cancer, the adjuvant use of trastuzumab and chemotherapy is well established, evaluated by no fewer than seven (NSABP [National Surgical Adjuvant Breast and Bowel Project] B-31, NCCTG [North Central Cancer Treatment Group] N9831, HERA [Herceptin Adjuvant], FinHER [Finland Herceptin], NOAH [Neo-Adjuvant Herceptin], FNCLCC-PACS [Fédération Nationale des Centres de Lutte Contre le Cancer–Programmes d'Actions Concertées Sein] 04, and BCIRG [Breast Cancer International Research Group] 006)[1-7] prospective randomized trials (Table 1). The last of these trials to be published, BCRIG 006, was a comparison of each of two different chemotherapy-trastuzumab combinations, one of which contained anthracycline-based chemotherapy (ACTH) and one of which did not (TCH), against a chemotherapy (ACT) control.[7] Although the study was not designed to compare the two trastuzumab-based arms, many looked to BCIRG 006 to provide sufficient evidence for abandoning the use of anthracyclines in HER2-positive breast cancer, because this issue emerged as the "most important"[7(p1280)] aspect of the trial. On the basis of the superiority of both trastuzumab-containing regimens to the chemotherapy-only control, the absence of a statistically significant difference between the two trastuzumab-containing arms, and the difference in toxicities between those two arms, the BCIRG investigators concluded that the "risk-benefit ratio favored the nonanthracycline TCH regimen over ACT plus trastuzumab."[7(p1273)] Many, if not most, US oncologists seem to agree. After presentations of the BCIRG 006 study, the TCH regimen was approved in 2008 by the US Food and Drug Administration; it now accounts for the majority of adjuvant trastuzumab-based chemotherapy in the United States.[8]

With the publication of BCIRG 006, it is appropriate for clinicians, patients, and investigators to ask whether TCH represents the preferred regimen for HER2-positive breast cancer. For a number of reasons, we believe it is not. A critical limitation is that BCIRG 006 was not powered to show equivalence or even noninferiority between the two trastuzumab-based regimens and thus lacked the ability to demonstrate a modest but potentially important difference between the two regimens. In fact, there were numerically fewer recurrences and deaths in the ACTH arm than in the TCH arm, an observation that invites the possibility that an adequately powered trial might not have concluded that the regimens were similar in their ability to prevent recurrence. Indeed, the data (Table 1) indicated a persistent 3% absolute improvement in disease-free survival favoring ACTH through 5 years of follow-up (84% with ACTH; 81% with TCH; 75% with ACT and no trastuzumab), a difference observed in both node-negative and node-positive patients. Similarly, the hazard ratio for ACTH versus ACT (0.64 [36% risk reduction]; $P < .001$) was consistently superior to that seen for TCH versus ACT (0.75 [25% risk reduction]; $P = .04$). The BCIRG trial had only a 75% power to show a 36% improvement with ACTH over TCH; with this design, there is a real possibility that superiority for ACTH over TCH might have been missed.

Aside from BCIRG 006, there have been no other direct comparisons between ACTH and TCH. However, a retrospective, single-institution experience suggested higher rates of complete pathologic

Table 1. Trials of Adjuvant Trastuzumab for HER2-Positive Breast Cancer

Study and Sample Size for Trial Results	Treatment Schema	DFS HR *v* Chemotherapy Alone	DFS *P*	OS HR *v* Chemotherapy Alone	OS *P*	Actuarial DFS (%)
Trials of Concurrent Chemotherapy and Trastuzumab						
NSABP B-31/NCCTG N9831 (N = 4,045)[1]	Doxorubicin plus cyclophosphamide followed by paclitaxel *v*	0.52	< .001	0.61	< .001	73.7*
	Doxorubicin plus cyclophosphamide followed by paclitaxel with trastuzumab → extended trastuzumab†					85.7*
FinHER (N = 232)[3]	Docetaxel or vinorelbine followed by fluorouracil plus epirubicin plus cyclophosphamide *v*	0.42	.02	0.41	.07	78‡
	Docetaxel or vinorelbine with trastuzumab followed by fluorouracil plus epirubicin plus cyclophosphamide					89‡
NOAH (N = 235)[5]§	Doxorubicin plus paclitaxel followed by paclitaxel followed by cyclophosphamide plus methotrexate plus fluorouracil *v*	0.59	.013	0.62	.114	56‡
	Doxorubicin plus paclitaxel followed by paclitaxel followed by cyclophosphamide plus methotrexate plus fluorouracil, all with trastuzumab → extended trastuzumab†					71‡
BCIRG 006 (N = 3,222)[7]	Doxorubicin plus cyclophosphamide followed by docetaxel *v*	0.64	< .001	0.63	< .001	75‖
	Doxorubicin plus cyclophosphamide followed by docetaxel with trastuzumab → extended trastuzumab† *v*					84‖
	Docetaxel plus carboplatin with trastuzumab → extended trastuzumab†	0.75	.04	0.77	.04	81‖
Trials of Sequential Chemotherapy and Trastuzumab						
HERA (N = 3,401)[2]	Chemotherapy¶ *v*	0.76	< .001	0.85	.11	72.2*
	Chemotherapy → extended trastuzumab†¶					78.6*
NCCTG N9831 (N = 2,184)[6]	Doxorubicin plus cyclophosphamide followed by paclitaxel *v*	0.69	< .001	0.88	.343	71.8‖
	Doxorubicin plus cyclophosphamide followed by paclitaxel → extended trastuzumab†					80.1‖
FNCLCC-PACS04 (N = 528)[4]	Fluorouracil plus epirubicin plus cyclophosphamide or epirubicin plus docetaxel *v*	0.86	.41	1.27	NS	78‡
	Fluorouracil plus epirubicin plus cyclophosphamide or epirubicin plus docetaxel → extended trastuzumab†					81‡

Abbreviations: BCIRG, Breast Cancer International Research Group; DFS, disease-free survival; FinHer, Finland Herceptin; FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; HER2, human epidermal growth factor receptor 2; HERA, Herceptin Adjuvant; HR, hazard ratio; NCCTG, North Central Cancer Treatment Group; NOAH, Neo-Adjuvant Herceptin; NS, nonsignificant; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; PACS, Programmes d'Actions Concert ées Sein.

*4-year DFS.

†Total duration of trastuzumab = 1 year.

‡3-year DFS.

§Chemotherapy administered as neoadjuvant treatment.

‖5-year DFS.

¶At least four cycles of standard chemotherapy; 92% of patients received anthracyclines.

response, and better long-term rates of tumor control, for patients with HER2-positive tumors who received neoadjuvant anthracycline-based and weekly taxane-based trastuzumab regimens compared with those who received TCH.[9] Given the statistical features of BCIRG 006, the actual breast cancer event rates, and indirect data from another study, it seems that BCIRG 006 neither established the equivalence of TCH to ACTH nor excluded the real possibility that the anthracycline-based ACTH regimen was more active than the nonanthracycline option. Such a possibility might be crucial to women with HER2-positive breast cancer, particularly those at moderate to high risk of developing recurrent disease.

A second substantial limitation centers on the chemotherapy backbones of the control and experimental treatment arms. The control arm in BCIRG 006 included anthracyclines, because data from a number of sources, albeit in the pretrastuzumab era, have supported the importance of anthracyclines in HER2-positive breast cancer. Retrospective subset analyses of anthracycline-based adjuvant chemotherapy studies have suggested the major benefit for anthracycline-based regimens is seen in HER2-overexpressing tumors,[10] and the addition of taxanes to anthracyclines is clearly beneficial in HER2-positive breast cancers.[11] By contrast, the importance of carboplatin—the C in TCH—as adjuvant therapy is unknown. Its inclusion in the TCH regimen arose from preclinical models that suggested synergy between platinum- and taxane-based chemotherapy and trastuzumab,[12] a hypothesis not borne out in prospective clinical trials of HER2-positive metastatic breast cancer, which showed no significant

difference in outcomes seen with TH compared with TCH.[13] Meanwhile, the ACTH regimen in BCIRG 006 employed a chemotherapy treatment schedule that may have been less effective than other anthracycline- and taxane-based dosing schedules. For instance, dose-dense scheduling of anthracyclines and taxanes is superior to treatments administered every 3 weeks,[14] as was done in BCIRG 006. This difference notably includes the superiority of weekly paclitaxel to every-3-week taxane schedules.[15] Indeed, weekly paclitaxel is a chemotherapy option with marked activity as adjuvant treatment when administered after anthracyclines and concurrently with trastuzumab.[6] These observations are reminders that the foundation for ACTH-type regimens is grounded on the inherent value of each treatment component and suggest that optimizing each of them might yield even better treatment outcomes.

Besides expression of HER2 itself, there is no selection marker that predicts benefit with trastuzumab or other HER2-directed treatments. The topoisomerase II alpha gene (*TOP2A*), amplified in 30% to 40% of patient cases of HER2-positive breast cancer, has been associated with sensitivity to anthracycline-based chemotherapy in some trials.[16] In the subset of patients in BCIRG 006 whose tumors had *TOP2A* coamplification, each of the three treatment arms (ACT, ACTH, and TCH) yielded similar results, implying "no incremental benefit"[7(p1278)] to adding trastuzumab to anthracycline-based chemotherapy. Among patients without *TOP2A* coamplification, those treated with trastuzumab did better. However, a similar analysis from NSABP B-31 found that adding trastuzumab to anthracycline-based chemotherapy significantly reduced recurrence risk, regardless of *TOP2A* status.[17] These mixed findings imply that *TOP2A* should not at present be used to select the adjuvant chemotherapy regimen or decide whether to offer trastuzumab.

It is essential to consider tradeoffs between efficacy and adverse effects when selecting an adjuvant regimen, and with anthracyclines, the greatest concern is cardiomyopathy. The risk of generally reversible congestive heart failure is clearly increased when trastuzumab is administered with or after anthracyclines. In an attempt to gauge the relative impact of this toxicity, the BCIRG investigators developed a posthoc therapeutic index for critical clinical events, which included distant metastatic recurrence, heart failure, and acute leukemia. Among the 1,075 women in each treatment arm, the numeric advantage of ACTH over TCH in preventing breast cancer recurrence (124 *v* 144 patients) was offset in the therapeutic index by the greater risk of grade 3 or 4 heart failure (21 *v* four patients); there was a single case of leukemia in each of these treatments arms. However, at the time of analysis, not a single patient had died as a result of heart failure. Indeed, the 1% numeric difference in overall survival between the arms, translating to approximately 10 patients and favoring ACTH, clearly suggests that the toxicities of ACTH did not compromise the overall survival of patients in that arm and that a survival advantage remains within the realm of possibility for patients treated with anthracyclines. Furthermore, the design of the index equated cancer metastasis with an episode of congestive heart failure, a weighting that was not borne out by the respective severity of these conditions nor necessarily in the preferences of patients or clinicians.

Clearly, concern about cardiomyopathy justifies the development of regimens that minimize cardiac toxicity. The BCIRG 006 data provide valuable information for patients and clinicians weighing this risk in the context of choosing adjuvant treatments. Established risk factors for trastuzumab-related cardiac dysfunction identified in other adjuvant trials have included older age (> 60 or 65 years), borderline ejection fraction (left ventricular ejection fraction of 50% to 55%), and pre-existing hypertension.[18] Conversely, women lacking these risk factors have an approximate 1% risk of heart failure resulting from anthracycline- and trastuzumab-based treatment.

Beyond the risk of clinical congestive heart failure, a substantial fraction of patients have experienced asymptomatic changes in ejection fraction with ACTH. These reversible, clinically silent but measurable drops in cardiac ejection fraction have been seen in patients receiving anthracyclines when careful sequential measurements of ejection fraction have been obtained. However, the clinical meaning of these asymptomatic changes, along with their persistence, has not been fully defined in either the short or long term. Other prospective experiences treating patients with dose-dense, every-2-week AC followed by paclitaxel and trastuzumab have not shown declines in average left ventricular ejection fraction through 18 months of follow-up.[19] Although it remains unclear how to use clinical criteria to select patients for specific trastuzumab-based treatments, we are ambivalent about forfeiting a greater chance for breast cancer cure because of a chance of cardiomyopathy or subclinical changes in ejection fraction.

It is quite possible that trastuzumab and other anti-HER2–specific therapies are the trump cards that render obsolete the question of choosing the best chemotherapy for HER2-positive tumors. We anticipate a time when our tools for risk stratification and treatment selection are substantially refined, allowing more tailored approaches to individual choices of adjuvant therapy. Ideally, we would like to minimize or ultimately eliminate the use of anthracyclines or any toxic treatment that has not been proven necessary. We anticipate that progress in diagnostic tests and therapeutics will ultimately enable many patients with HER2-positive breast cancer to avoid chemotherapy altogether in favor of better, biologically focused treatments. Until more data are available, however, we encourage patients and clinicians to consider the most highly studied, highly effective adjuvant trastuzumab regimens—those that also incorporate anthracycline treatments—as the mainstay of therapy for women with higher-risk HER2-positive tumors. To date, such regimens offer the greatest chance of preventing breast cancer recurrence. Certainly, among patients at moderate to high risk of recurrence who do not have specific cardiac risk factors, the tradeoffs of efficacy and cardiotoxicity seem likely to justify the anthracycline-based treatment. For women with lower-risk HER2-positive tumors, in whom marginal differences in treatment outcome are possibly less critical, or women with clinical reasons for preferring to avoid anthracyclines, TCH is an effective and important alternative option.

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REFERENCES

1. Perez EA, Romond EH, Suman VJ, et al: Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: Joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 29:3366-3373, 2011

2. Gianni L, Dafni U, Gelber RD, et al: Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: A 4-year follow-up of a randomised controlled trial. Lancet Oncol 12:236-244, 2011

3. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al: Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 354:809-820, 2006

4. Spielmann M, Roché H, Delozier T, et al: Trastuzumab for patients with axillary node-positive breast cancer: Results of the FNCLCC-PACS 04 trial. J Clin Oncol 27:6129-6134, 2009

5. Gianni L, Eiermann W, Semiglazov V, et al: Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): A randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 375:377-384, 2010

6. Perez EA, Suman VJ, Davidson NE, et al: Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. J Clin Oncol 29:4491-4497, 2011

7. Slamon D, Eiermann W, Robert N, et al: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273-1283, 2011

8. Bergstrom KA, Wang Z, Aksamit I, et al: Guideline adherence rates of chemotherapy treatment for breast cancer patients treated in U.S. community oncology practices. Presented at the 2010 American Society of Clinical Oncology Breast Cancer Symposium, Washington, DC, October 1-3, 2010

9. Bayraktar S, Gonzalez-Angulo AM, Lei X, et al: Efficacy of neoadjuvant therapy with trastuzumab concurrent with anthracycline- and nonanthracycline-based regimens for HER2-positive breast cancer. Cancer 118:2385–2393, 2012

10. Gennari A, Sormani MP, Pronzato P, et al: HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: A pooled analysis of randomized trials. J Natl Cancer Inst 100:14-20, 2008

11. Hayes DF, Thor AD, Dressler LG, et al: HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 357:1496-1506, 2007

12. Pegram MD, Konecny GE, O'Callaghan C, et al: Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. J Natl Cancer Inst 96:739-749, 2004

13. Valero V, Forbes J, Pegram MD, et al: Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): Two highly active therapeutic regimens. J Clin Oncol 29:146-156, 2011

14. Citron ML, Berry DA, Cirincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:431-439, 2003

15. Sparano JA, Wang M, Martino S, et al: Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358:1663-1671, 2008

16. Press M, Sauter G, Boyce M, et al: Alteration of topoisomerase II-alpha gene in human breast cancer: Association with responsiveness to anthracycline-based chemotherapy. J Clin Oncol 29:859-867, 2011

17. Gianni L, Norton L, Wolmark N, et al: Role of anthracyclines in the treatment of early breast cancer. J Clin Oncol 27:4798-4808, 2009

18. Tan-Chiu E, Yothers G, Romond E, et al: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2–overexpressing breast cancer: NSABP B-31. J Clin Oncol 23:7811-7819, 2005

19. Morris PG, Chen C, Steingart R, et al: Troponin I and C-reactive protein are commonly detected in patients with breast cancer treated with dose-dense chemotherapy incorporating trastuzumab and lapatinib. Clin Cancer Res 17:3490-3499, 2011

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