Adjuvant Trastuzumab in HER2-Positive Breast Cancer

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Abstract

BACKGROUND—Trastuzumab improves survival in the adjuvant treatment of HER-positive breast cancer, although combined therapy with anthracycline-based regimens has been associated with cardiac toxicity. We wanted to evaluate the efficacy and safety of a new nonanthracycline regimen with trastuzumab.

METHODS—We randomly assigned 3222 women with HER2-positive early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). The primary study end point was disease-free survival. Secondary end points were overall survival and safety.

RESULTS—At a median follow-up of 65 months, 656 events triggered this protocol-specified analysis. The estimated disease-free survival rates at 5 years were 75% among patients receiving AC-T, 84% among those receiving AC-T plus trastuzumab, and 81% among those receiving TCH. Estimated rates of overall survival were 87%, 92%, and 91%, respectively. No significant differences in efficacy (disease-free or overall survival) were found between the two trastuzumab

regimens, whereas both were superior to AC-T. The rates of congestive heart failure and cardiac dysfunction were significantly higher in the group receiving AC-T plus trastuzumab than in the TCH group (P<0.001). Eight cases of acute leukemia were reported: seven in the groups receiving the anthracycline-based regimens and one in the TCH group subsequent to receiving an anthracycline outside the study.

CONCLUSIONS—The addition of 1 year of adjuvant trastuzumab significantly improved disease-free and overall survival among women with HER2-positive breast cancer. The risk–benefit ratio favored the nonanthracycline TCH regimen over AC-T plus trastuzumab, given its similar efficacy, fewer acute toxic effects, and lower risks of cardiotoxicity and leukemia. (Funded by Sanofi-Aventis and Genentech; BCIRG-006 ClinicalTrials.gov number, NCT00021255.)

The her2 gene encodes a tyrosine kinase receptor that mediates critical signaling functions in normal and malignant breast epithelial cells.[1] An acquired alteration consisting of amplification and overexpression of the gene product occurs in approximately 20 to 25% of human breast cancers.[2,3] HER2 overexpression is associated with an aggressive clinical pheno-type that includes high-grade tumors, increased growth rates, early systemic metastasis, and decreased rates of disease-free and overall survival.[2,3] Preclinical data indicate that this adverse clinical picture results from fundamental changes in the biologic features of breast-cancer cells containing the alteration, including increased proliferation, suppression of apoptosis, increased motility, greater invasive and metastatic potential, accelerated angiogenesis, and steroid hormone independence.[4–11]

In previous studies, many of these HER2-mediated adverse characteristics were reversed by the use of monoclonal antibodies directed against the tyrosine kinase receptor,[10,12–15] and these data led to phase 1 testing of a murine anti-HER2 monoclonal antibody, 4D5.[16] Preliminary efficacy and safety data prompted the development of a humanized monoclonal antibody to produce trastuzumab.[17] Alone and in combination with chemotherapy, trastuzumab has been shown to have an acceptable safety record and to be active in advanced HER2-positive disease.[18–20] Subsequently, in a large, randomized study, the addition of trastuzumab to chemotherapy yielded significant improvements in rates of objective response, response duration, and time to disease progression (56%, 58%, and 65% improvement, respectively), as well as a 30% improvement in the rate of overall survival among patients with first-line metastatic disease.[21] A significant side effect was an increase by a factor of 4 in the rate of cardiac dysfunction, including congestive heart failure, especially when trastuzumab was used in combination with anthracycline-based regimens.[21]

These data led to the initial regulatory approval of trastuzumab for metastatic HER2-positive breast cancer and resulted in its evaluation in early-stage disease. Five randomized trials (four large and one small) were then launched to evaluate the efficacy and safety of adjuvant therapy with trastuzumab, and findings in three of these trials have been reported.[22–24] One report contained results from similar treatment groups in two studies.[23] All three large studies used trastuzumab in combination either exclusively or predominantly with anthracycline-based regimens,[22,23] and all showed a significant benefit of trastuzumab, with a reduction in the rate of recurrence of approximately 50% and improvement in the rate of survival of approximately 30%.[22,23] Again, an increase by a factor of 4 to 5 in the rate of congestive heart failure was noted when adjuvant trastuzumab was used with anthracyclines, and an even larger proportion of patients had subclinical loss of left ventricular function.[22,23,25,26]

In the fourth large study, the Breast Cancer International Research Group 006 (BCIRG-006) trial, we also evaluated adjuvant therapy with trastuzumab but included a second trastuzumab-containing regimen, which did not have an anthracycline. This new regimen, consisting of docetaxel, carboplatin, and trastuzumab (TCH), is based on preclinical

synergies observed between trastuzumab and platinum salts or docetaxel that were not seen with anthracyclines or paclitaxel.[14,27,28] It was also anticipated that TCH might circumvent the cardiac toxicity seen with anthracycline-based regimens.[21] Phase 2 and 3 trials of TCH in patients with advanced disease showed that this regimen resulted in the longest period of progression-free survival reported to date, with rare cardiac dysfunction.[18–20] A trial comparing TCH with docetaxel plus trastuzumab in metastatic disease showed no significant difference in progression-free survival between these two regimens.[29] However, the dose of docetaxel was 33% higher in the group receiving docetaxel plus trastuzumab than in the group receiving TCH (100 mg per square meter of body-surface area vs. 75 mg per square meter). The only trial that directly evaluated the added benefit of carboplatin in a dose-equivalent, taxane-containing regimen showed that TCH had a significant advantage with respect to progression-free survival over paclitaxel plus trastuzumab.[19] For these reasons, we decided to evaluate TCH in addition to an anthracycline-based regimen in adjuvant treatment of HER2-positive breast cancers. We report efficacy and safety results from this study in an intention-to-treat analysis of data from all 3222 patients.

METHODS

PATIENTS AND STUDY DESIGN

From April 2001 through March 2004, we randomly assigned 3222 women with HER2-positive, invasive, high-risk, node-negative or node-positive adenocarcinoma (stage T1, T2, or T3) from 41 countries to receive a standard adjuvant anthracycline–taxane chemotherapy regimen, the same regimen plus trastuzumab, or a new non-anthracycline, trastuzumab-based regimen (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Specific demographic and clinical characteristics of patients were similar in the three study groups (Table 1). The HER2-positive status of all tumors was confirmed with the use of fluorescence in situ hybridization (PathVision, Abbott) before randomization.

In the first group, women received standard therapy with doxorubicin (60 mg per square meter) and cyclophosphamide (600 mg per square meter) every 3 weeks for four cycles, followed by docetaxel (100 mg per square meter) every 3 weeks for four doses (AC-T). In the second group, patients received AC-T plus trastuzumab, beginning with the first dose of docetaxel and continuing for 1 year (AC-T plus trastuzumab). In the third group, patients received docetaxel (75 mg per square meter) plus carboplatin (area under the curve, 6 mg per milliliter per minute), given every 3 weeks for six cycles concurrently with trastuzumab, followed by trastuzumab for an additional 34 weeks (TCH). In the two trastuzumab-containing regimens, trastuzumab was initially administered at a dose of 4 mg per kilogram of body weight, followed by 2 mg per kilogram per week during chemotherapy and then 6 mg per kilogram every 3 weeks to complete 1 year of trastuzumab treatment. Hematopoietic growth factors were used at the discretion of treating physicians.

The institutional review board at each institution approved the study. All patients provided written informed consent.

PRIMARY AND SECONDARY END POINTS

The study's primary end point was disease-free survival, which was defined as the time from randomization to breast-cancer recurrence, a second primary cancer (excluding contralateral ductal carcinoma in situ), or death from any cause, whichever came first. Secondary end points included overall survival, global safety, and cardiac safety.

CARDIAC SAFETY

In addition to monitoring general safety, we instituted an intense cardiac-monitoring schedule. We measured the left ventricular ejection fraction (LVEF) in each patient seven times throughout the study to detect congestive heart failure or sustained asymptomatic subclinical loss of mean LVEF, which was defined as a relative reduction from baseline of more than 10% at the last follow-up evaluation (Section 2 in the Supplementary Appendix). An independent cardiac review panel whose members were unaware of study-group assignments reviewed all cases of suspected cardiac events. In addition, we calculated and reported the mean LVEF in each study group, measured at protocol-defined times, along with 95% confidence intervals.

TOP2A COAMPLIFICATION

We also evaluated the effect on efficacy of a second alteration within the HER2 amplicon that imparts incremental anthracycline sensitivity to a subset of HER2-positive cancers. The prespecified analysis of the gene encoding topoisomerase II alpha (*TOP2A*) showed that coamplification of this gene occurs in 35% of HER2-positive cancers. These data, together with the methods used, have been reported previously.[30] When present, *TOP2A* coamplification is associated with the incremental benefit previously described for anthracycline as compared with nonanthracycline regimens in HER2-positive breast cancers.[31,32]

STUDY OVERSIGHT

The study was conducted in accordance with the protocol, which is available at NEJM.org. The breast steering committee of the BCIRG study group, which was composed entirely of academic investigators, designed the study and collected and analyzed all the data. The trial advisory committee consisted of one member from each sponsor and six members of the BCIRG breast steering committee. The resulting report was written by the first author and reviewed by the steering committee, who made the decision to submit the manuscript for publication. All authors vouch for the accuracy and completeness of the data. The sponsor and major funder of the study was Sanofi-Aventis, with additional support provided by Genentech. Trastuzumab was provided by Genentech free of charge for study patients in the United States and was purchased by Sanofi-Aventis for all study patients in other countries. Docetaxel was provided by Sanofi-Aventis for all study patients.

STATISTICAL ANALYSIS

We used log-rank tests to compare disease-free survival and overall survival in the three study groups and plotted Kaplan–Meier product-limit estimators. We planned to conduct three protocol-specified interim analyses and a final analysis after observing 300, 450, 650, and 900 events, respectively, according to an O'Brien–Fleming group sequential boundary. The significance levels (alpha) for these analyses were equal to approximately 0.0002, 0.0030, 0.0111, and 0.0461, respectively. At each analysis, a step-down testing procedure was used. We compared the AC-T group with each trastuzumab-containing regimen (AC-T plus trastuzumab and TCH) at a significance level equal to one half alpha to account for multiple testing. If both comparisons were significant, we compared the two trastuzumab regimens at a significance equal to alpha.

The first interim analysis was carried out after the observation of 322 disease-free survival events in September 2005. At that time, the efficacy boundaries were crossed and showed a significant difference in disease-free survival events in favor of both AC-T plus trastuzumab and TCH, as compared with AC-T, with no significant difference between AC-T plus trastuzumab and TCH. Here, we present the results of the third protocol-specified analysis.

For this protocol-specified analysis (656 events), the study had a power of 80% to detect a hazard ratio of 0.75 or less for the comparison of either of the two trastuzumab-containing regimens with AC-T and a power of 75% to detect a hazard ratio of 0.64 or less for the comparison of AC-T plus trastuzumab with TCH. All reported P values are two-sided. All analyses were conducted by the International Institute for Drug Development and were performed with the use of SAS statistical software, version 9.0 (SAS Institute). The results of all analyses were presented to an independent data and safety monitoring committee.

RESULTS

PRIMARY AND SECONDARY END POINTS

At the time of this analysis, 656 disease-free survival events were observed (257 in the group receiving AC-T, 185 in the group receiving AC-T plus trastuzumab, and 214 in the group receiving TCH). At this point, 348 patients had died during a median follow-up of 65 months. For both primary and secondary efficacy end points, a significant benefit with respect to disease-free and overall survival was seen in both groups treated with trastuzumab-containing regimens, as compared with the group that received AC-T (standard therapy), which had a 5-year rate of disease-free survival of 75% (Fig. 1A) and a rate of overall survival of 87% (Fig. 2 in the Supplementary Appendix). For patients receiving AC-T plus trastuzumab, the 5-year rate of disease-free survival was 84% (hazard ratio for the comparison with AC-T, 0.64; P<0.001), and the rate of overall survival was 92% (hazard ratio, 0.63; P<0.001). For patients receiving TCH, the 5-year rate of disease-free survival was 81% (hazard ratio, 0.75; P = 0.04), and the rate of overall survival was 91% (hazard ratio, 0.77; P = 0.04). In contrast, no significant difference in the rate of disease-free or overall survival was seen between the two trastuzumab-containing regimens. However, the study was not powered to detect equivalence between these two regimens.

Analyses of absolute between-group differences, stratified according to nodal status and tumor size, were also performed. These analyses showed that among node-negative patients, the estimated rates of disease-free survival at 5 years were significantly improved by trastuzumab, with a rate of 93% in the group receiving AC-T plus trastuzumab and 90% in the group receiving TCH, as compared with 85% in the group receiving AC-T (hazard ratio for AC-T plus trastuzumab, 0.47; P = 0.003; hazard ratio for TCH, 0.64; P = 0.06) (Table 1A in the Supplementary Appendix).

Among node-positive patients, trastuzumab also significantly improved 5-year rates of disease-free survival, which were 80% in the group receiving AC-T plus trastuzumab and 78% in the group receiving TCH, as compared with 71% in the group receiving AC-T (hazard ratio for AC-T plus trastuzumab, 0.68; P<0.001; hazard ratio for TCH, 0.78; P = 0.01) (Table 1A in the Supplementary Appendix). In addition, a benefit of trastuzumab was seen in node-positive patients at highest risk for recurrence (i.e., those with ≥4 positive nodes), for whom the 5-year rate of disease-free survival was 73% in the group receiving AC-T plus trastuzumab and 72% in the group receiving TCH, as compared with 61% in the group receiving AC-T (hazard ratio, 0.66; P = 0.002 for both comparisons) (Table 1A in the Supplementary Appendix).

Analysis of the efficacy of trastuzumab on the basis of the size of the primary tumor showed similarly significant benefits for patients with small or large primary tumors, with no significant between-group differences among patients with tumors of intermediate size (Table 1B in the Supplementary Appendix). Among patients with HER2-positive tumors measuring 1 cm or less in the greatest diameter, the estimated 5-year rates of disease-free survival were 86% in the group receiving AC-T plus trastuzumab and 86% in the group receiving TCH, as compared with 72% in the group receiving AC-T (hazard ratio for AC-T

plus trastuzumab, 0.36; P = 0.03; hazard ratio for TCH, 0.45; P = 0.09) (Table 1B in the Supplementary Appendix). For tumors measuring 1 cm or more but no more than 2 cm, the analysis showed no significant difference in 5-year rates of disease-free survival, with rates of 87% in the group receiving AC-T plus trastuzumab and 86% in the group receiving TCH, as compared with 86% in the group receiving AC-T (hazard ratio for AC-T plus trastuzumab, 0.88; P = 0.59; hazard ratio for TCH, 1.11; P = 0.64) (Table 1B in the Supplementary Appendix). For tumors measuring 2 cm or more at diagnosis, the 5-year rates of disease-free survival were 82% in the group receiving AC-T plus trastuzumab and 79% in the group receiving TCH, as compared with 71% in the group receiving AC-T (hazard ratio for AC-T plus trastuzumab, 0.62; P<0.001; hazard ratio for TCH, 0.70; P<0.001) (Table 1B in the Supplementary Appendix). Forest-plot analyses also showed improved efficacy for both trastuzumab-containing regimens, as compared with standard therapy, with respect to rates of disease-free and overall survival in subgroups defined according to nodal status (negative vs. positive), hormone-receptor results (negative vs. positive), and tumor size (≤2 cm vs. >2 cm) (Fig. 3A through 3D in the Supplementary Appendix).

Overall, among the 3222 patients who underwent randomization, there were only 29 more primary events in the TCH group (214 events) than in the group receiving AC-T plus trastuzumab (185 events). A comparison of the therapeutic indexes of the two trastuzumab-containing regimens and the standard-therapy regimen was performed on the basis of the numbers of distant breast-cancer recurrences, cases of congestive heart failure, and cases of acute leukemia occurring in each study group (Table 2). In this comparison, the difference between the trastuzumab-containing regimens was even smaller than the difference in the number of primary events.

TOP2A Coamplification

Among patients with HER2-positive breast cancers without *TOP2A* coamplification, the diseasefree survival benefit with trastuzumab-containing regimens was even greater than that seen in the overall analysis of all patients (191 patients in the group receiving AC-T, 119 in the group receiving AC-T plus trastuzumab, and 130 in the group receiving TCH) (Fig. 1A and 1B). However, in the 35% of HER2-positive cancers in which *TOP2A* was coamplified, the rates of disease-free survival for the trastuzumab-containing regimens were virtually indistinguishable from the rate with standard therapy (55 patients in the group receiving AC-T, 52 in the group receiving AC-T plus trastuzumab, and 72 in the group receiving TCH) (Fig. 1C). This subpopulation of patients appears to derive no incremental benefit from trastuzumab, even though the therapeutic index favors TCH over the anthracycline-based regimen because of better short- and long-term toxicity profiles (Tables 2, 3, and 4).

Adverse Effects

General Safety—We monitored side effects of the adjuvant chemotherapy regimens as well as specific toxic effects that were linked to individual agents. All toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). A significant difference favoring the group receiving TCH, as compared with the group receiving AC-T plus trastuzumab, was noted for arthralgias, myalgias, the hand–foot syndrome, stomatitis, and vomiting (Table 3). Significant differences in sensory and motor neuropathies, nail changes, and myalgias also favored the TCH group. The incidences of neutropenia and leukopenia were significantly lower in the TCH group than in the group receiving AC-T plus trastuzumab, whereas the incidences of anemia and thrombocytopenia were significantly lower in the group receiving AC-T plus trastuzumab than in the TCH group. Finally, acute leukemias developed in seven patients who were receiving anthracycline-based regimens and in one patient who was receiving TCH. However, in this

patient, leukemia was diagnosed after the patient had received an anthracycline for the treatment of a B-cell lymphoma that occurred after her breast cancer. None of these patients had a breast-cancer recurrence, and at the time of this report, five of the eight patients with leukemia had died.

Cardiac Safety—At study entry, cardiac risk factors were well balanced among the three study groups (Table 4). At the time of this analysis, the incidence of congestive heart failure in the two trastuzumab-containing regimens was higher in the group receiving AC-T plus trastuzumab (2.0%) than in the AC-T group (0.7%) or the TCH group (0.4%); the incidence with AC-T plus trastuzumab as compared with TCH was increased by a factor of 5. The difference in rates of congestive heart failure between the two trastuzumab-containing regimens significantly favored TCH over AC-T plus trastuzumab (P<0.001). In addition, a significant difference in sustained, subclinical loss of mean LVEF (defined as >10% relative loss) was observed in the group receiving AC-T plus trastuzumab, as compared with the TCH group (18.6% vs. 9.4%, P<0.001), with a rate of 11.2% in the AC-T group. Although the cardiac dysfunction associated with trastuzumab after the use of adjuvant anthracyclines has been reported to be relatively transient,[22–26] in this study, the subclinical toxic effect persisted for several years (Fig. 2). Of 194 of the 1042 patients (19%) who had a relative reduction in LVEF of more than 10% in the group receiving AC-T plus trastuzumab, the decrease persisted for at least 4 years after randomization in 33% of the patients. Of note, 23 of 1073 patients (2.1%) who were assigned to receive AC-T plus trastuzumab never received trastuzumab because the LVEF declined to an unacceptable level after the initial anthracycline treatment. Consequently, these HER2-positive women received no targeted therapy after receiving anthracycline therapy.

Discussion

The rationale supporting the adjuvant use of trastuzumab is derived from an improved understanding of the molecular diversity of human breast cancer[2,3,21,33] and recognition that this disease should not be treated with the one-size-fits-all approach that has characterized most approaches to adjuvant chemotherapy for the past four decades. The significant efficacy shown by trastuzumab in treating first-line metastatic HER2-positive breast cancer[21] prompted its evaluation in early-stage disease. This study is one of four large, randomized adjuvant trials undertaken as part of this evaluation. Like the previously reported studies,[22–24] our study showed improvements in efficacy with the adjuvant use of trastuzumab. The major safety issue that we observed was increased cardiac dysfunction when trastuzumab was used in combination with anthracycline-based chemotherapy, a finding that is also concordant with the results of previous studies.[22,23,25,26]

Despite these similarities, there are three distinct differences between our study and the other trials of adjuvant trastuzumab. First, we performed the intention-to-treat analyses of efficacy and safety as originally and prospectively defined in the study protocol; no statistical modifications or study-group exclusions were permitted for combined or early analyses of data. Second, after the initial efficacy results for adjuvant trastuzumab were reported in April 2005, only 23 patients (2.1%) in the control group (i.e., those receiving AC-T) crossed over to receive trastuzumab before reaching prespecified study end points. This permitted unbiased long-term comparisons of both efficacy and safety among the three study groups. Third, and perhaps most important, our study was the only one to include a nonanthracycline chemotherapy regimen.

Almost all current adjuvant therapies incorporate the use of anthracyclines on the basis of the meta-analysis by the Early Breast Cancer Trialists' Group, which showed an improved efficacy of anthracycline-containing chemotherapy regimens over regimens without an

anthracycline.[34] However, analyses of HER2 status among approximately 5200 patients who participated in eight large, randomized adjuvant trials comparing anthracycline with nonanthracycline chemotherapy regimens showed that only women with HER2-positive breast cancer derived an incremental benefit from anthracycline use.[35–39] No incremental benefit was apparent for the 75 to 80% of breast cancers that were HER2-negative. A meta-analysis of these and additional data has been reported.[40] Detailed data derived from an analysis of the *TOP2A* gene in our study showed that *TOP2A* coamplification occurred in 35% of HER2-positive patients and was directly associated with the incremental benefit that anthracyclines provide over nonanthracycline regimens in HER2-positive disease.[30] The use of a non-anthracycline (TCH) regimen in our study allowed us to ask whether preclinical synergies observed between platinum-based chemotherapy and trastuzumab, as well as between docetaxel and trastuzumab,[15,27] might compensate for the incremental efficacy advantage of anthracyclines in HER2-positive breast cancers. Although our study was not powered to detect equivalence between the two trastuzumab-containing groups, outcome data showed that TCH had similar efficacy (with respect to disease-free and overall survival) despite the omission of anthracyclines and the use of two rather than three cytotoxic drugs. In our study, this phenomenon was shown even in patients who are thought to be at highest risk for recurrence (i.e., those with ≥4 positive lymph nodes or a primary tumor measuring >2 cm at diagnosis). Moreover, although the overall numerical advantage (29 disease-free survival events) in favor of AC-T plus trastuzumab over TCH was not significant, this difference in efficacy came at the cost of a highly significant increase in congestive heart failure (21 cases vs. 4 cases). These differences in rates of congestive heart failure were not taken into account in any of the protocol-specified efficacy comparisons. In addition, our findings show that the use of AC-T plus trastuzumab resulted in a significantly increased risk of sustained subclinical loss in LVEF. Finally, the use of TCH had the pragmatic advantage of allowing patients to complete all adjuvant chemotherapy in 12 rather than 16 weeks, as well as allowing them to complete 12 months of trastuzumab therapy 12 weeks sooner and requiring fewer infusion visits.

The emerging further understanding of long-term and life-altering toxic effects associated with adjuvant anthracyclines may provide the most compelling support for nonanthracycline regimens. The well-known, long-term side effects of anthracyclines include significantly increased risks of congestive heart failure,[41,42] myelodysplasia, and acute leukemia.[43] However, recent analyses of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database indicate that we may be underestimating the full effect of anthracycline use on long-term cardiac and hematologic health in patients treated for breast cancer with these agents,[41–43] possibly because the majority of adjuvant studies have been designed primarily to evaluate differences in efficacy and have used follow-up periods of 7 to 10 years for both efficacy and safety analyses. Attempts to obtain longer-term safety data, including cardiac outcomes, are systematically biased by loss of later follow-up.

In addition, the SEER database is derived from information on women 65 years of age or older. The mean age of women in the HER2-positive adjuvant studies was 51 to 52 years, whereas the mean age of the overall breast-cancer population is approximately 62 years. Given that data from our study and other trials[22,23,25,26] show that trastuzumab augments the incidence of anthracycline-associated congestive heart failure and subclinical loss of LVEF, the full effect of any nonsymptomatic damage induced by the combination of trastuzumab with anthracycline-based regimens may not be apparent until much later as these younger women have additional, age-related cardiac insults. Our findings on long-term, subclinical LVEF losses, as well as the published results from the SEER database analyses,[41–43] involving some 42,000 women, support this concern.

Furthermore, although myeloid growth factors permit delivery of full-dose, accelerated-schedule adjuvant anthracycline-cyclophosphamide treatments, registry data suggest a doubling of the incidences of acute leukemia and myelodysplasia associated with these regimens, though the absolute risk remains low.[43] Of note, all cases of acute leukemia in our study occurred in patients who had previously been exposed to an anthracycline. Some observers have argued that these major toxic effects are rare and are offset by significant efficacy gains obtained with anthracyclines. However, our data do not fully support this argument. We did not find any significant incremental therapeutic benefits of combined trastuzumab-anthracycline treatment as compared with TCH, yet we did see significant increases in both acute and chronic toxic effects with the trastuzumab-anthracycline regimen. Consequently, we believe that TCH offers an effective alternative to the anthracycline-based regimens and their associated risks.

An improved understanding of the molecular basis of malignant disease is allowing the development of rational treatment strategies that are more effective and less toxic than traditional empiric regimens. The identification and characterization of the HER2 alteration in a subset of human breast cancers and the subsequent development of trastuzumab represent the practical realization of this translational ideal. Our findings show that we can further exploit this new translational knowledge to optimize efficacy while simultaneously minimizing acute and chronic toxic effects in the adjuvant treatment of HER2-positive breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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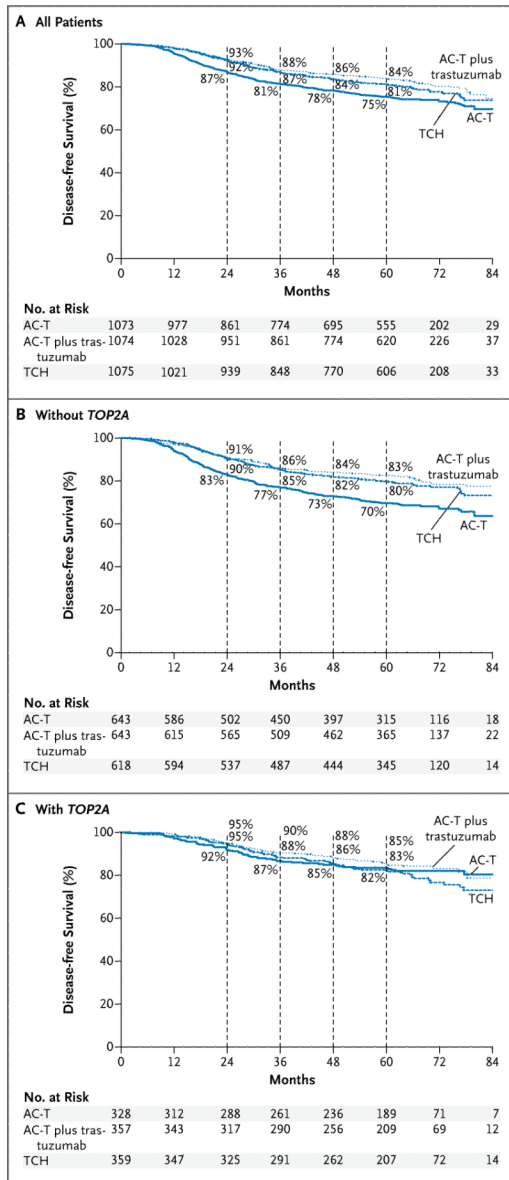
Figure 1. Disease-free Survival among All Patients and According to *TOP2A* Status
Shown are the results of Kaplan–Meyer analyses of relative rates of disease-free survival
among all study patients (Panel A), those without coamplification of the gene encoding
topoisomerase II alpha (*TOP2A*) (Panel B), and those with coamplification of *TOP2A* (Panel
C). AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH
docetaxel, carboplatin, and trastuzumab.

Figure 2. Left Ventricular Ejection Fraction (LVEF) at 48 Months
Shown are the values for the mean left ventricular ejection fraction for 3086 of 3222 patients
(96%) in the three study groups. At the time of this analysis, sufficient numbers of LVEF
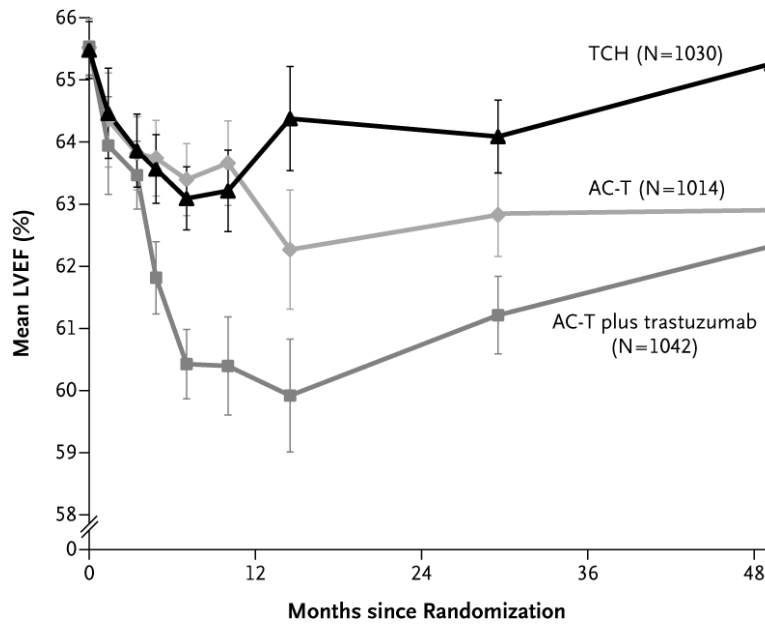determinations were not yet available beyond 48 months. AC-T denotes doxorubicin and
cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and
trastuzumab.

Table 1

Baseline Characteristics of the Patients.[*]

Characteristic	AC-T (N = 1073)	AC-T plus Trastuzumab (N = 1074)	TCH (N = 1075)
	number of patients (percent)		
Age <50 yr	562 (52)	559 (52)	577 (54)
Karnofsky performance score of 100[†]	856 (80)	853 (79)	862 (80)
Mastectomy	638 (59)	675 (63)	642 (60)
Radiotherapy	718 (67)	723 (67)	729 (68)
Hormonal therapy	531 (49)	542 (50)	541 (50)
No. of positive nodes			
0	309 (29)	306 (28)	307 (29)
1 to 3	413 (38)	410 (38)	415 (39)
4 to 10	235 (22)	259 (24)	249 (23)
>10	116 (11)	99 (9)	104 (10)
Tumor size[‡]			
≤2 cm	439 (41)	413 (38)	431 (40)
>2 to 5 cm	566 (53)	591 (55)	574 (53)
>5 cm	67 (6)	70 (7)	68 (6)
Positive for estrogen receptor, progesterone receptor, or both	576 (54)	578 (54)	579 (54)

[*] There were no significant differences among the three groups. AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab. ■j- A Karnofsky score of 100 indicates no measurable loss of performance status.

[‡] The tumor size was unavailable for one patient in the AC-T group and two patients in the TCH group.

Table 2

Therapeutic Index for Critical Clinical Events.[*]

Clinical Event	AC-T	AC-T plus Trastuzumab	TCH
		number of events	
Total events	201	146	149
Distant breast-cancer recurrence	188	124	144
Grade 3 or 4 congestive heart failure	7	21	4
Acute leukemia	6	1	1[†]

[*] This therapeutic index is a compilation of the numbers of distant breast-cancer recurrences, cases of congestive heart failure, and cases of acute leukemia. AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab.

[†] This case of acute leukemia developed after the patient received an anthracy-cline as part of a combination chemotherapy regimen for a diffuse large B-cell lymphoma that occurred after she received treatment with TCH for breast cancer.

Table 3

Adverse Events.[*]

Event	AC-T (N = 1050)	AC-T plus Trastuzumab (N = 1068)	TCH (N = 1056)	P Value[†]
		number of patients (percent)		
Grade 3 or 4 nonhematologic events				
Arthralgia	34 (3.2)	35 (3.3)	15 (1.4)	0.006
Myalgia	55 (5.2)	56 (5.2)	19 (1.8)	<0.001
Fatigue	73 (7.0)	77 (7.2)	76 (7.2)	1.0
Hand-foot syndrome	20 (1.9)	20 (1.9)	0	<0.001
Stomatitis	37 (3.5)	31 (2.9)	15 (1.4)	0.02
Diarrhea	32 (3.0)	60 (5.6)	57 (5.4)	0.85
Nausea	62 (5.9)	61 (5.7)	51 (4.8)	0.38
Vomiting	65 (6.2)	72 (6.7)	37 (3.5)	<0.001
Irregular menses	284 (27.0)	260 (24.3)	280 (26.5)	0.25
Specific nonhematologic events				
Neuropathy, any grade				
Sensory	510 (48.6)	531 (49.7)	380 (36.0)	<0.001
Motor	55 (5.2)	67 (6.3)	45 (4.3)	0.04
Nail changes, any grade	518 (49.3)	466 (43.6)	303 (28.7)	<0.001
Myalgia, any grade	555 (52.9)	593 (55.5)	411 (38.9)	<0.001
Renal failure, any grade	0	0	1 (0.1)	0.50
Grade 3 or 4 creatinine elevation[‡]	6 (0.6)	3 (0.3)	1 (0.1)	0.62
Grade 3 or 4 hematologic events				
Neutropenia	665 (63.3)	764 (71.5)	696 (65.9)	0.01
Leukopenia	544 (51.8)	644 (60.3)	509 (48.2)	<0.001
Febrile neutropenia	98 (9.3)	116 (10.9)	101 (9.6)	0.35
Neutropenic infection	117 (11.1)	127 (11.9)	118 (11.2)	0.63
Anemia	25 (2.4)	33 (3.1)	61 (5.8)	<0.001
Thrombocytopenia	17 (1.6)	22 (2.1)	64 (6.1)	<0.001
Leukemia	6 (0.6)	1 (0.1)	1 (0.1)	1.0

[*] AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab.

[†] P values are for the comparison between the group receiving AC-T plus trastuzumab and the group receiving TCH.

[‡] Grade 3 or 4 creatinine elevation was defined according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Table 4

Cardiac Risk Factors and Events.[*]

Variable	AC-T (N = 1073)	AC-T plus Trastuzumab (N = 1074)	TCH (N = 1075)
	number of patients (percent)		
Risk factors			
Diabetes	38 (3.5)	36 (3.4)	28 (2.6)
Hypertension	178 (16.6)	178 (16.6)	190 (17.7)
Obesity[†]	214 (19.9)	242 (22.5)	234 (21.8)
Hypercholesterolemia	54 (5.0)	47 (4.4)	43 (4.0)
Left-side radiotherapy	378 (35.2)	349 (32.5)	364 (33.9)
Events			
Cardiac-related death	0	0	0
Congestive heart failure[‡]	7 (0.7)	21 (2.0)	4 (0.4)[§]
>10% relative reduction in left ventricular ejection fraction[¶]	114 (11.2)[∥]	194 (18.6)	97 (9.4)[**]

[*] AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab.

[†] Obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more.

[‡] This condition was defined as New York Heart Association grade 3 or 4 congestive heart failure.

[§] $P<0.001$ for the comparison between the group receiving AC-T plus trastuzumab and the TCH group.

[¶] Results in this category are for 1018 patients receiving AC-T, 1042 patients receiving AC-T plus trastuzumab, and 1031 patients receiving TCH.

[∥] $P<0.001$ for the comparison between the group receiving AC-T plus trastuzumab and the AC-T group.

[**] $P<0.001$ for the comparison between the group receiving AC-T plus trastuzumab and the TCH group.