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USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

ABSTRACT

Background The *HER2* gene, which encodes the growth factor receptor HER2, is amplified and HER2 is overexpressed in 25 to 30 percent of breast cancers, increasing the aggressiveness of the tumor.

Methods We evaluated the efficacy and safety of trastuzumab, a recombinant monoclonal antibody against HER2, in women with metastatic breast cancer that overexpressed HER2. We randomly assigned 234 patients to receive standard chemotherapy alone and 235 patients to receive standard chemotherapy plus trastuzumab. Patients who had not previously received adjuvant (postoperative) therapy with an anthracycline were treated with doxorubicin (or epirubicin in the case of 36 women) and cyclophosphamide with (143 women) or without trastuzumab (138 women). Patients who had previously received adjuvant anthracycline were treated with paclitaxel alone (96 women) or paclitaxel with trastuzumab (92 women).

Results The addition of trastuzumab to chemotherapy was associated with a longer time to disease progression (median, 7.4 vs. 4.6 months; $P<0.001$), a higher rate of objective response (50 percent vs. 32 percent, $P<0.001$), a longer duration of response (median, 9.1 vs. 6.1 months; $P<0.001$), a lower rate of death at 1 year (22 percent vs. 33 percent, $P=0.008$), longer survival (median survival, 25.1 vs. 20.3 months; $P=0.046$), and a 20 percent reduction in the risk of death. The most important adverse event was cardiac dysfunction, which occurred in 27 percent of the group given an anthracycline, cyclophosphamide, and trastuzumab; 8 percent of the group given an anthracycline and cyclophosphamide alone; 13 percent of the group given paclitaxel and trastuzumab; and 1 percent of the group given paclitaxel alone. Although the cardiotoxicity was potentially severe and, in some cases, life-threatening, the symptoms generally improved with standard medical management.

Conclusions Trastuzumab increases the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER2. (N Engl J Med 2001; 344:783-92.)

DESPITE advances in the diagnosis and treatment of breast cancer, more than 44,000 women in the United States will die this year of metastatic disease.[1,2] Although objective responses to some chemotherapy regimens are common, few patients with metastatic disease are cured,[3,4] and treatments frequently cause substantial adverse effects.

A growth factor receptor gene,[5-7] human epidermal growth factor receptor (*HER2*), is amplified in 25 to 30 percent of breast cancers and in these cases the encoded protein is present in abnormally high levels in the malignant cells.[8,9] Women with breast cancers that overexpress HER2 have an aggressive form of the disease with significantly shortened disease-free survival and overall survival.[8-12] Laboratory studies indicate that amplification of *HER2* has a direct role in the pathogenesis of these cancers,[13-17] thereby providing investigators with an opportunity to target a therapeutic agent directly against the alteration.

Several murine monoclonal antibodies against the extracellular domain of the HER2 protein were found to inhibit the proliferation of human cancer cells that overexpressed HER2, both in vitro and in vivo.[18-20] To minimize immunogenicity, the antigen-binding region of one of the more effective antibodies was

From the Division of Hematology and Oncology, UCLA School of Medicine, Los Angeles (D.J.S., M.P.); the Department of Oncology, McGill University, Montreal (B.L.-J.): Medical Affairs, Genentech, South San Francisco, Calif. (S.S., V.P., A.B.); IntraBiotics, Mountain View, Calif. (H.F.); the Department of Biostatistics, University of Washington, Seattle (T.F.); the Department of Obstetrics and Gynecology, Frauenklinik vom Roten Kreuz, Munich, Germany (W.E.); the Department of Oncology, Rush–Presbyterian–St. Luke's Medical Center, Chicago (J.W.); the Department of Oncology, Hospital General Universitari Vall d'Hebron, Barcelona, Spain (J.B.); and the Department of Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York (L.N.). Address reprint requests to Dr. Slamon at UCLA School of Medicine, Division of Hematology/Oncology, 11-244 Factor Bldg., 10833 Le Conte, Los Angeles, CA 90095-1678, or at dslamon@mednet.ucla.edu.

*Additional study investigators are listed in the Appendix.

fused to the framework region of human IgG[21] and tested against breast-cancer cells that overexpressed HER2 in vitro and in vivo.[21,22] This antibody, called trastuzumab, inhibited tumor growth when used alone[4] but had synergistic effects[20,22-24] when used in combination with cisplatin and carboplatin,[20,23] docetaxel,[24] and ionizing radiation[25] and additive effects when used with doxorubicin, cyclophosphamide, methotrexate, and paclitaxel.[22-26]

Phase 1 clinical trials showed that the antibody is safe and confined to the tumor (unpublished data). Subsequent phase 2 trials demonstrated that many women with *HER2*-positive metastatic disease who had relapsed after chemotherapy had a response to trastuzumab[27,28]; as suggested by the preclinical data, the efficacy of trastuzumab when given with chemotherapy was superior to its effectiveness when used alone.[28,29] We report the results of a phase 3 trial in which women with cancers that overexpressed HER2 who had not previously received chemotherapy for metastatic disease were randomly assigned to receive either chemotherapy alone or chemotherapy plus trastuzumab. The primary end points of the study were the time to disease progression and the incidence of adverse effects. Secondary end points were the rates and the duration of responses, the time to treatment failure, and overall survival.

METHODS

Patients

Women with progressive metastatic breast cancer that overexpressed HER2 who had not previously received chemotherapy for metastatic disease were eligible for the study. Written informed consent was obtained from all patients. The level of expression of HER2 was determined by immunohistochemical analysis in a central laboratory. Only patients who had weak-to-moderate staining of the entire tumor-cell membrane for HER2 (referred to as a score of 2+) or more than moderate staining (referred to as a score of 3+) in more than 10 percent of tumor cells on immunohistochemical analysis were eligible for the study.

Patients were excluded if they had bilateral breast cancer, untreated brain metastases, osteoblastic bone metastases, pleural effusion or ascites as the only evidence of disease, a second type of primary cancer, or a Karnofsky score of less than 60. Patients were also excluded if they were pregnant or had received any type of investigational agent within 30 days before the study began.

Treatments

Patients were randomly assigned to receive either chemotherapy alone or chemotherapy plus trastuzumab. Chemotherapy consisted of an anthracycline (doxorubicin at a dose of 60 mg per square meter of body-surface area or epirubicin at a dose of 75 mg per square meter) plus cyclophosphamide (at a dose of 600 mg per square meter) for patients who had never before received an anthracycline, or paclitaxel (at a dose of 175 mg per square meter) for patients who had received adjuvant (postoperative) anthracycline. Doxorubicin or epirubicin plus cyclophosphamide or paclitaxel was administered once every three weeks for six cycles, and additional cycles were administered at the investigator's discretion. Trastuzumab was administered intravenously in a loading dose of 4 mg per kilogram of body weight, followed by a dose of 2 mg per kilogram once a week, until there was evidence of disease progression. On the detection of disease progression, patients were given the option of entering a nonrandomized, open-label study in which trastuzumab was administered at the same doses alone or in combination with other therapies. Sixty-six percent of such patients elected to do so.

Efficacy

Patients were evaluated for a response at weeks 8 and 20 and then at 12-week intervals. The determinations were made by the members of an independent response-evaluation committee, who were unaware of the patients' treatment assignments. A complete response was defined as the disappearance of all tumor on the basis of radiographic evidence, visual inspection, or both. A partial response was defined as a decrease of more than 50 percent in the dimensions of all measurable lesions. Disease progression was defined as an increase of more than 25 percent in the dimensions of any measurable lesion. The primary study end point was the time to disease progression. Prespecified secondary end points were the rate of objective response, the duration of a response, the time to treatment failure (a composite of disease progression, death, discontinuation of treatment, and the use of other types of antitumor therapy), and survival as of October 1999.

Adverse Events

Clinical assessments were performed at base line, at specified times, and at the time the patient was removed from the study. Adverse events were classified as mild, moderate, or severe. An independent cardiac evaluation committee whose members were unaware of patients' treatment assignments assessed the incidence, severity, treatment, and outcome of cardiac dysfunction. Abnormalities in laboratory values were classified by the grading system of the World Health Organization and cardiac dysfunction by the criteria of the New York Heart Association.

Statistical Analysis

We estimated that 450 patients would be needed in order for the study to detect at a power of 90 percent a 50 percent increase in the median time to disease progression, given a median time to progression of eight months in the subgroups receiving chemotherapy alone and a significance level of 0.05 with the use of a two-tailed log-rank test. All end points were analyzed according to the intention-to-treat principle. The primary analysis of all efficacy variables was performed on data pooled from both chemotherapy regimens. Additional analyses were performed within each chemotherapy group. The time to the various end points was analyzed with the use of Kaplan–Meier methods, and a two-sided log-rank test was used to compare the groups. The rate of objective response was analyzed with the use of normal approximation methods; a two-sided chi-square test was used to compare the groups.

RESULTS

Characteristics of the Patients

We enrolled 469 patients between June 1995 and March 1997 (Table 1); 5 patients were never treated: 2 declined treatment, 1 died before treatment was begun, 1 had disease progression at enrollment, and 1 was enrolled inadvertently. The median time in the study was 40 weeks (range, 1 to 127) in the group given chemotherapy plus trastuzumab, as compared with 25 weeks (range, 1 to 131) in the group given chemotherapy alone, reflecting the longer time to disease progression in the group that received combination treatment. The median number of doses of trastuzumab was 36 (range, 1 to 98).

The base-line characteristics of the patients were similar among the treatment groups. Stratification

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)*	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)†	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Age — yr				
Mean ±SD	54±10.3	54±10.1	51±11.5	51±11.0
Range	27–76	25–75	25–77	26–73
Karnofsky score — no./no. analyzed (%)				
90–100	91/138 (66)	89/135 (66)	68/90 (76)	61/94 (65)
60–80	47/138 (34)	46/135 (34)	22/90 (24)	33/94 (35)
Median no. of positive lymph nodes at diagnosis	1.0	0.5	5.0	6.0
Prior therapy — no./no. analyzed (%)				
Adjuvant chemotherapy	81/142 (57)	50/136 (37)	88/91 (97)	95/95 (100)
Hormonal therapy (as adjuvant, for metastasis, or both)	88/142 (62)	76/134 (57)	49/89 (55)	53/95 (56)
Radiotherapy (as adjuvant, for metastasis, or both)	69/143 (48)	76/136 (56)	60/89 (67)	72/95 (76)
Median disease-free interval — mo	24.5	22.8	22.4	18.9
Degree of overexpression of HER2 — no./no. analyzed (%)‡				
2+	35/143 (24)	42/138 (30)	24/92 (26)	19/96 (20)
3+	108/143 (76)	96/138 (70)	68/92 (74)	77/96 (80)
No. of metastatic sites at enrollment — no./no. analyzed (%)				
≤1	48/143 (34)	49/136 (36)	31/91 (34)	27/95 (28)
2	38/143 (27)	48/136 (35)	32/91 (35)	35/95 (37)
≥3	57/143 (40)	39/136 (29)	28/91 (31)	33/95 (35)

*Twenty of these patients received epirubicin rather than doxorubicin.

†Sixteen of these patients received epirubicin rather than doxorubicin.

‡A score of 2+ indicated that more than 10 percent of tumor cells had weak-to-moderate staining of the entire membrane for HER2 on immunohistochemical analysis, and a score of 3+ that more than 10 percent of tumor cells had more than moderate staining for HER2 on immunohistochemical analysis.

on the basis of a history of adjuvant anthracycline treatment resulted in differences between the subgroups given an anthracycline and cyclophosphamide and the subgroups given paclitaxel. Patients who received paclitaxel had more involved lymph nodes at diagnosis and were more likely to have received adjuvant high-dose chemotherapy with stem-cell or marrow support than patients who received an anthracycline and cyclophosphamide. Of the 235 patients who received trastuzumab, 216 (92 percent) received at least 80 percent of the planned infusions and fewer than 5 percent required a delay in treatment or a reduction in doses of the chemotherapy. The final analysis of the primary end points was performed nine months after the enrollment of the last patient. Survival was analyzed 31 months after enrollment ended. The median duration of follow-up was 30 months (range, 30 to 51).

Efficacy

The median time to disease progression in the group assigned to chemotherapy plus trastuzumab was 7.4 months, whereas in the group given chemotherapy alone it was 4.6 months ($P<0.001$) (Table 2 and Fig. 1). This difference was evident in both the subgroup that received an anthracycline, cyclophosphamide, and trastuzumab (median time to progression, 7.8 months, as compared with 6.1 months in the subgroup given only an anthracycline and cyclophosphamide; $P<0.001$) and the subgroup that received paclitaxel and trastuzumab (median time to progression, 6.9 months, as compared with 3.0 months in the group given paclitaxel alone; $P<0.001$) (Fig. 1).

As compared with chemotherapy alone, treatment with chemotherapy plus trastuzumab was associated with a significantly higher rate of overall response (50 percent vs. 32 percent, $P<0.001$), a longer duration of response (median, 9.1 vs. 6.1 months; $P<0.001$), and a longer time to treatment failure (median, 6.9 vs. 4.5 months; $P<0.001$) (Tables 2 and 3). Statistically significant differences in the overall rates of response, the duration of response, and time to treatment failure were also found in the subgroup treated with an anthracycline, cyclophosphamide, and trastuzumab and the subgroup treated with paclitaxel and trastuzumab, as compared with the subgroups treated with an anthracycline and cyclophosphamide alone or paclitaxel alone, respectively (Tables 2 and 3).

TABLE 2. RESULTS OF AN INTENTION-TO-TREAT ANALYSIS OF THE END POINTS.*

END POINT	CHEMOTHERAPY PLUS TRASTUZUMAB (N=235)	EITHER TYPE OF CHEMOTHERAPY ALONE (N=234)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Median time to disease progression — mo	7.4	4.6	7.8	6.1	6.9	3.0
P value	<0.001		<0.001		<0.001	
Relative risk of progression (95% CI)	0.51 (0.41–0.63)		0.62 (0.47–0.81)		0.38 (0.27–0.53)	
Median time to treatment failure — mo	6.9	4.5	7.2	5.6	5.8	2.9
P value	<0.001		<0.001		<0.001	
Relative risk of treatment failure (95% CI)	0.58 (0.47–0.70)		0.67 (0.52–0.86)		0.46 (0.33–0.63)	
Median survival — mo	25.1	20.3	26.8	21.4	22.1	18.4
P value	0.046		0.16		0.17	
Relative risk of death (95% CI)	0.80 (0.64–1.00)		0.82 (0.61–1.09)		0.80 (0.56–1.11)	

*The time to treatment failure was defined as the time from randomization to disease progression, discontinuation of treatment for any reason, use of other types of antitumor therapy, or death. The final analysis of the primary end point (time to disease progression) was performed nine months after enrollment of the last patient. The most recent survival data were obtained 31 months after the enrollment of the last patient, with a median follow-up of 35 months (range, 30 to 51). As of the data-cutoff date of December 31, 1997, a total of 388 (83 percent) of the 469 patients had discontinued the study, including 173 (74 percent) of the 235 patients assigned to receive chemotherapy plus trastuzumab and 215 (92 percent) of the 234 patients assigned to receive chemotherapy alone. The response-evaluation committee assessed the tumor response in 446 patients: 99 percent of the 452 patients who had an assessment after the base-line evaluation and 95 percent of the 469 patients who enrolled in the study. In the group given paclitaxel and trastuzumab, the increase in the interval between randomization and disease progression was greater among patients who had a Karnofsky score of 90 or more at base line. The most common sites of disease progression among patients who received chemotherapy plus trastuzumab and among those who received chemotherapy alone were the liver (32 percent and 46 percent), the lungs (20 percent and 21 percent), bone (18 percent and 15 percent), and the central nervous system (18 percent and 9 percent). CI denotes confidence interval.

The addition of trastuzumab was also associated with a significantly lower rate of death at one year (22 percent, as compared with 33 percent in the group given chemotherapy alone; P=0.008). The median survival was 25.1 months in the group given chemotherapy plus trastuzumab and 20.3 months in the group that received chemotherapy alone (P=0.046) (Table 2 and Fig. 2). This calculation included patients in the group given chemotherapy alone who received open-label trastuzumab after the occurrence of disease progression. The risk of death was reduced by 18 to 20 percent in the subgroups given trastuzumab (Table 2). The efficacy of trastuzumab was consistently observed in both subgroups; however, patients with a score of 3+ for the overexpression of HER2 benefited to a greater degree from such treatment than those with a score of 2+.

Deaths

As of October 1999, 314 patients had died (149 in the group given chemotherapy plus trastuzumab and 165 in the group given chemotherapy alone); 95 percent of these deaths were attributed to progressive disease. Two deaths, both in patients who had received an anthracycline, cyclophosphamide, and trastuzumab, were possibly related to trastuzumab therapy: one patient died of sepsis after 2 doses of trastuzumab, and the second died of hepatitis B–related hepatorenal syndrome after 11 doses of trastuzumab.

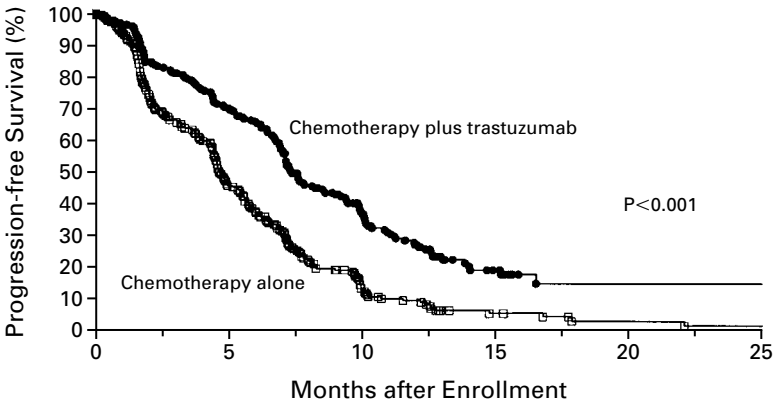
Adverse Events

Approximately 25 percent of patients had chills, fever, or both during the initial infusion of trastuzumab. Slowing the infusion rate ameliorated these symptoms. No episodes of frank anaphylaxis occurred, but one patient had moderate hypotension, and three had mild bronchospasm, all of which resolved without treatment.

Infection occurred in 47 percent of patients who were given chemotherapy plus trastuzumab and in 29 percent of those treated with chemotherapy alone (Table 4). These infections consisted of mild-to-moderate infections of the upper respiratory tract in 72 percent of cases, catheter-related infections in 9 percent, a viral syndrome in 3 percent, and other types of infections in 16 percent. Of the 14 catheter-related

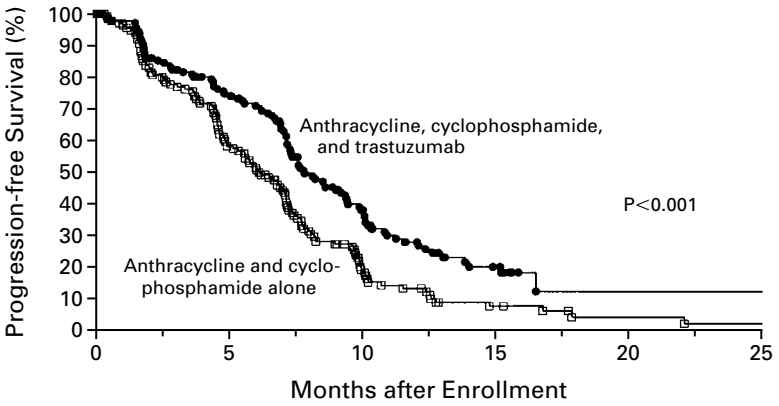
Figure 1 (facing page). Kaplan–Meier Estimates of Progression-free Survival, According to Whether Patients Were Randomly Assigned to Receive Chemotherapy plus Trastuzumab or Chemotherapy Alone (Panel A), and Whether Chemotherapy Consisted of Either a Combination of an Anthracycline and Cyclophosphamide (Panel B) or Paclitaxel (Panel C).

A



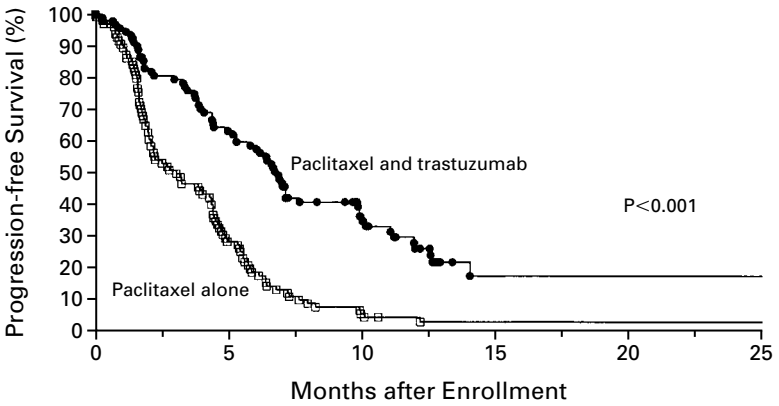
No. at Risk				
Chemotherapy plus trastuzumab	235	152	63	15
Chemotherapy alone	234	103	25	6

B



No. at Risk				
Anthracycline, cyclophosphamide, and trastuzumab	143	98	40	12
Anthracycline and cyclophosphamide alone	138	77	20	6

C



No. at Risk			
Paclitaxel and trastuzumab	92	54	23
Paclitaxel alone	96	26	5

TABLE 3. RATES AND DURATIONS OF RESPONSES.*

VARIABLE	CHEMOTHERAPY PLUS TRASTUZUMAB (N=235)	CHEMOTHERAPY ALONE (N=234)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Complete response — no. (%)	18 (8)	8 (3)	11 (8)	6 (4)	7 (8)	2 (2)
Partial response — no. (%)	100 (43)	66 (28)	69 (48)	52 (38)	31 (34)	14 (15)
Complete and partial responses — no. (% [95% CI])	118 (50 [44–57])	74 (32 [26–38])	80 (56 [48–64])	58 (42 [34–50])	38 (41 [31–51])	16 (17 [9–24])
P value	<0.001		0.02		<0.001	
Median duration of response — mo	9.1	6.1	9.1	6.7	10.5	4.5
P value	<0.001		0.005		<0.01	

*The analysis included all 469 patients. A complete response was defined as the disappearance of all tumors on the basis of radiographic evidence, visual inspection, or both. A partial response was defined as a decrease in the dimensions of all measurable lesions of more than 50 percent. The duration of response was defined as the time from the first response to disease progression or death. The response-evaluation committee assessed the tumor response in 446 patients: 99 percent of the 452 patients who had an assessment after the base-line evaluation and 95 percent of the 469 patients who enrolled in the study. In the group given paclitaxel and trastuzumab, the response rate was higher among patients who had a Karnofsky score of 90 to 100 at base line. CI denotes confidence interval.

infections among patients who received trastuzumab, 3 were severe, 13 required treatment, and 4 required surgical removal of the catheter. The incidence of sepsis was low and evenly distributed among the four subgroups. The addition of trastuzumab to the chemotherapy regimen increased the frequency of leukopenia and anemia (Table 4). These cases of cytopenia were mild to moderate in severity and did not necessitate the discontinuation of trastuzumab or withdrawal from the study.

Twenty-five patients (19 in the subgroup given an anthracycline, cyclophosphamide, and trastuzumab and 6 in the subgroup given paclitaxel and trastuzumab) stopped taking trastuzumab because of adverse events. Eighteen patients (15 in the subgroup given an anthracycline, cyclophosphamide, and trastuzumab and 3 in the subgroup given paclitaxel and trastuzumab) had clinical signs of cardiac dysfunction. Two additional adverse events were attributed to trastuzumab therapy: an embolic stroke as a possible complication of cardiac dysfunction and chest pain after 49 doses of trastuzumab and six cycles of an anthracycline and cyclophosphamide. The events in the remaining five patients were not considered to be related to trastuzumab.

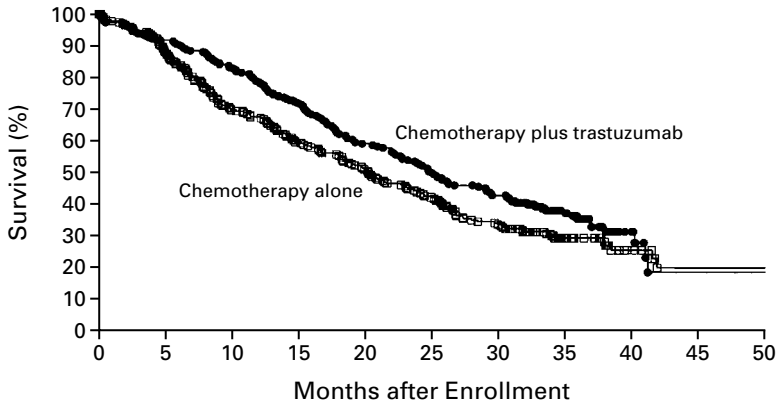
Cardiotoxicity

The adverse cardiac events prompted a retrospective analysis of all cases of cardiac dysfunction by an independent cardiac review and evaluation committee. This review identified 63 patients with symptomatic or asymptomatic cardiac dysfunction: 39 of 143 patients had received an anthracycline, cyclophosphamide, and trastuzumab (accounting for 27 percent of this subgroup); 11 of 135 had received an anthracycline and cyclophosphamide alone (incidence, 8 percent); 12 of 91 had received paclitaxel and trastuzumab (incidence, 13 percent); and 1 of 95 had received paclitaxel alone (incidence, 1 percent). Among these patients, the incidence of cardiac dysfunction of New York Heart Association class III or IV was highest among patients who had received an anthracycline, cyclophosphamide, and trastuzumab (16 percent, as compared with 3 percent among patients who had received an anthracycline and cyclophosphamide alone, 2 percent among those who had received paclitaxel and trastuzumab, and 1 percent among those who had received paclitaxel alone).

Of the 63 patients with cardiac dysfunction, 44 received standard medical treatment. The condition improved in 33 of these 44 patients, did not change in 5, and worsened in 4. One patient in the group given an anthracycline, cyclophosphamide, and trastuzumab died of cardiac dysfunction, as did one in the group given an anthracycline and cyclophosphamide alone. Among the five patients with persistent class III or IV cardiac dysfunction, three were in the group given an anthracycline, cyclophosphamide, and tras-

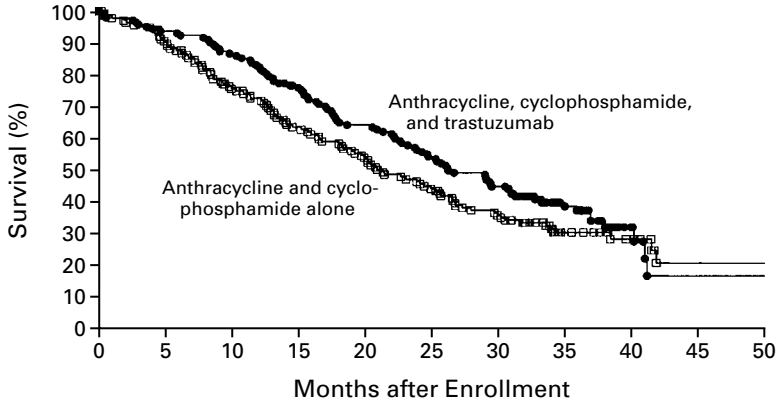
Figure 2 (facing page). Kaplan–Meier Estimates of Overall Survival, According to Whether Patients Were Randomly Assigned to Receive Chemotherapy plus Trastuzumab or Chemotherapy Alone (Panel A) and Whether Chemotherapy Consisted of Either a Combination of an Anthracycline and Cyclophosphamide (Panel B) or Paclitaxel (Panel C).

A



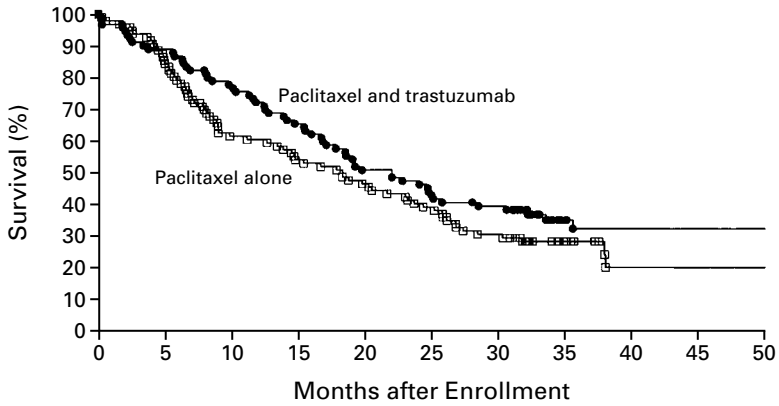
No. at Risk									
Chemotherapy plus trastuzumab	235	214	192	165	134	114	96	47	11
Chemotherapy alone	234	205	160	136	116	97	76	37	13

B



No. at Risk									
Anthracycline, cyclophosphamide, and trastuzumab	143	134	123	107	89	75	62	32	9
Anthracycline and cyclophosphamide alone	138	124	102	85	72	60	48	23	11

C



No. at Risk									
Paclitaxel and trastuzumab	92	80	69	58	45	39	34	15	2
Paclitaxel alone	96	81	58	51	44	37	28	14	2

TABLE 4. ADVERSE EVENTS THAT OCCURRED IN MORE THAN 10 PERCENT OF PATIENTS AS A GROUP.*

TYPE OR LOCATION OF ADVERSE EVENT	CHEMOTHERAPY PLUS TRASTUZUMAB (N=234)	CHEMOTHERAPY ALONE (N=230)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=135)	PACLITAXEL AND TRASTUZUMAB (N=91)	PACLITAXEL ALONE (N=95)
	percentage with event (percentage with severe event)					
Any type						
Abdominal pain	27 (3)	20 (3)	23 (2)	18 (2)	34 (3)	22 (4)
Asthenia	57 (7)	56 (7)	54 (7)	55 (7)	62 (8)	57 (8)
Back pain	31 (4)	22 (4)	27 (2)	16 (2)	36 (8)	30 (5)
Chest pain	24 (3)	24 (4)	20 (3)	21 (2)	30 (3)	27 (5)
Chills	38 (<1)	8 (<1)	35 (<1)	11 (2)	42 (1)	4 (0)
Fever	53 (8)	29 (4)	56 (11)	33 (7)	47 (2)	23 (1)
Headache	41 (4)	30 (4)	44 (3)	31 (5)	36 (7)	28 (2)
Infection	47 (2)	29 (2)	47 (2)	30 (2)	46 (1)	27 (2)
Pain	58 (6)	50 (7)	57 (4)	42 (8)	60 (10)	61 (6)
Heart failure	22 (10)	5 (2)	27 (16)	8 (3)	13 (2)	1 (1)
Digestive tract						
Anorexia	28 (<1)	22 (2)	31 (0)	26 (2)	24 (1)	16 (2)
Constipation	32 (1)	28 (3)	36 (2)	28 (3)	25 (0)	27 (2)
Diarrhea	45 (1)	27 (3)	45 (1)	25 (3)	45 (1)	30 (3)
Nausea	66 (5)	66 (7)	76 (6)	79 (10)	50 (3)	48 (3)
Stomatitis	22 (<1)	21 (0)	30 (1)	31 (3)	10 (0)	7 (0)
Vomiting	47 (5)	40 (7)	53 (3)	49 (8)	37 (9)	28 (5)
Hematologic and lymphatic systems						
Anemia	27 (2)	19 (2)	35 (3)	25 (2)	14 (1)	10 (1)
Leukopenia	41 (11)	26 (9)	52 (15)	33 (11)	24 (6)	17 (5)
Musculoskeletal system						
Arthralgia	20 (4)	14 (2)	8 (<1)	10 (<1)	37 (9)	21 (4)
Myalgia	23 (3)	22 (3)	13 (<1)	13 (<1)	38 (7)	36 (6)
Nervous system						
Paresthesia	29 (<1)	23 (<1)	17 (0)	11 (0)	47 (2)	39 (1)
Respiratory tract						
Increased coughing	43 (<1)	26 (<1)	43 (<1)	28 (0)	42 (0)	22 (1)
Dyspnea not related to heart failure	36 (3)	25 (3)	42 (4)	24 (4)	28 (1)	26 (1)
Pharyngitis	27 (0)	16 (<1)	30 (0)	18 (0)	22 (0)	14 (2)
Skin						
Alopecia	57 (26)	58 (35)	58 (25)	59 (42)	56 (26)	56 (26)
Rash	31 (<1)	17 (<1)	27 (0)	17 (<1)	38 (1)	18 (1)

*The analysis of adverse events excluded five patients who were never treated.

tuzumab. Increasing age was the only base-line characteristic that was a significant risk factor for cardiac dysfunction in patients who were receiving the combination of an anthracycline, cyclophosphamide, and trastuzumab. The cumulative dose of anthracycline was not identified as a risk factor, but this finding should be interpreted with caution, since the majority of patients received all six cycles of an anthracycline and cyclophosphamide as specified in the protocol. Adding trastuzumab to the chemotherapy regimen did not increase the risk of other adverse events related to chemotherapy, and in no patient were antibodies against trastuzumab detected.

DISCUSSION

We found that trastuzumab-based combination therapy was effective in that it reduced the relative risk of death by 20 percent at a median follow-up of 30 months. Few studies of metastatic breast cancer have demonstrated a survival advantage of this magnitude in association with the addition of a single agent.[30,31] Particularly noteworthy is that two thirds of patients who were initially assigned to receive chemotherapy alone began, after disease progression, to receive open-label trastuzumab alone or with chemotherapy. Such a crossover design would generally reduce the likelihood that a survival advantage would be found. Significant increases in the time to disease progression, the rates of response, the duration of responses, and the time to treatment failure were observed in both subgroups that were given chemotherapy plus trastuzumab. These results increased survival, an end point free of ascertainment bias.

The benefit of trastuzumab plus paclitaxel does not appear to be attributable to the poor outcomes in the group given paclitaxel alone. The rate of response of 17 percent among patients who were given paclitaxel alone is lower than the rate previously reported for

paclitaxel as an initial therapy for metastatic breast cancer.[32] Our patients, however, had a particularly poor prognosis related to the overexpression of HER2, the progression of disease after adjuvant therapy that included an anthracycline, and the receipt of prior treatment with high-dose chemotherapy followed by hematopoietic stem-cell rescue (in 22 percent).

The most troubling adverse effect of trastuzumab was cardiac dysfunction, a complication that had not been anticipated on the basis of the results of preclinical or early clinical studies.[20,23-29] We found that concurrent treatment with an anthracycline, cyclophosphamide, and trastuzumab significantly increased the risk of cardiac dysfunction, as compared with treatment with only an anthracycline and cyclophosphamide. A smaller increase in risk also occurred with treatment with paclitaxel and trastuzumab, as compared with treatment with paclitaxel alone, but all these patients had previously received an anthracycline. The 27 percent incidence of cardiac dysfunction among patients who were given an anthracycline, cyclophosphamide, and trastuzumab and the 13 percent incidence among those who were given paclitaxel and trastuzumab exceeded the expected incidence of less than 7 percent associated with cumulative doses of doxorubicin of up to 550 mg per square meter.[33]

Trastuzumab was discontinued because of cardiac dysfunction in 18 of 235 patients (8 percent) overall, and most of these patients received an anthracycline, cyclophosphamide, and trastuzumab. Continued use of trastuzumab did not cause further cardiac deterioration in most patients, and cardiac function improved in 75 percent of patients after the initiation of standard medical care. Among 81 patients who were assigned to receive an anthracycline and cyclophosphamide alone and who later received trastuzumab in an open-label fashion, clinically significant cardiac dysfunction developed in 7 (9 percent). The only significant risk factor associated with cardiac dysfunction was older age. The mechanism of the cardiotoxicity of trastuzumab is unknown.

Given the extremely poor prognosis of patients with HER2-positive metastatic breast cancer, the cardiotoxicity of trastuzumab must be weighed against its potential clinical benefit. We recommend a cautious approach to the use of trastuzumab in patients who have previously received anthracyclines and in those who are currently receiving anthracyclines. The adjuvant (postoperative) use of trastuzumab will be an important research topic, but since many patients with early-stage breast cancer can be cured by surgery and radiotherapy, the cardiotoxicity of trastuzumab will be a critical consideration. In this context, the risks of trastuzumab will necessitate great caution in its use, especially when it is combined with an anthracycline. Indeed, one large upcoming trial of adjuvant trastuzumab will evaluate a non-anthracycline-based regimen for this reason.[22-24]

The results of this phase 3 clinical trial indicate that trastuzumab, when added to conventional chemotherapy, can benefit patients with metastatic breast cancer that overexpresses HER2. As compared with the best available standard chemotherapy, concurrent treatment with trastuzumab and first-line chemotherapy was associated with a significantly longer time to disease progression, a higher rate of response, a longer duration of response, and improved overall survival. If confirmed in additional studies of patients with HER2-positive metastatic breast cancer, our results may affect treatment of this disease.

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APPENDIX

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