Anthracycline and Trastuzumab in Breast Cancer Treatment

This study was designed to evaluate the cardiac safety of the combined treatment of HER2-positive metastatic breast cancer patients with trastuzumab (Herceptin) plus epirubicin and cyclophosphamide (EC) in comparison with EC alone in HER2-negative metastatic breast cancer patients. Patients included those with metastatic breast cancer without any prior anti-HER2 treatment, anthracycline therapy, or any other chemotherapy for metastatic disease. This was a nonrandomized, prospective, dose-escalating, multicenter, open-label, phase II study in Germany. A control group of 23 patients received EC 90/600 mg/m2 3-weekly for six cycles (EC90 alone). A total of 26 HER2-positive patients were treated with trastuzumab, or H (2 mg/kg weekly after an initial loading dose of 4 mg/kg), and EC 60/600 mg/m2 3-weekly for six cycles (EC60+H); another 25 HER2-positive patients received H and EC 90/600 mg/m2 3-weekly for six cycles. Asymptomatic reductions in left ventricular ejection fraction (LVEF) of more than 10% points were detected in 12 patients (48%) treated with EC60 + H and in 14 patients (56%) treated with EC90 + H vs 6 patients (26%) in the EC90 alone cohort. LVEF decreases to 60%, vs 26% for EC90 alone. The interim results of this study suggest the cardiac safety of the combination of H with EC may be greater than that of H with AC (doxorubicin [Adriamycin]/cyclophosphamide); however, studies in larger numbers of patients are warranted. The combination regimen revealed promising efficacy.

The gene encoding the human epidermal growth factor receptor-2 (HER2) is amplified and the protein overexpressed in 20% to 25% of breast cancers.[1-3] This pathologic over-expression is associated with aggressive disease and poor prognosis.[4-6] In addition to its prognostic significance, HER2 positivity may have predictive value for response to chemotherapy regimens such as CMF (cyclophosphamide [Cytoxan, Neosar], methotrexate, fluorouracil [5-FU]), hormonal therapy, anthracyclines, and taxanes.[7-9] The occurrence of pathologic overexpression of HER2 in breast cancer[10] led to the development of the humanized anti-HER2 monoclonal antibody trastuzumab (Herceptin).[11] Trastuzumab monotherapy is both active and well tolerated in women with HER2-positive metastatic breast cancer (MBC), both first line[12] and in those who have progressed after receiving chemotherapy for MBC.[13] Nonrandomized treatment increases the objective response rate (from 32% to 50%) and extends time to progression (4.6 to 7.4 months) when used as first-line therapy in combination with doxorubicin (Adriamycin)/cyclophosphamide (AC) or paclitaxel in women with HER2-positive MBC.[14] Response rate and survival duration (56% and 26.8 months) were greatest in patients treated with trastuzumab plus AC compared to chemotherapy alone. Combining trastuzumab with AC was associated with a greater risk of cardiotoxicity than AC alone in this trial (27% vs 8%).[14,15] Cardiotoxicity manifested as asymptomatic decreases in left ventricular ejection fraction (LVEF) with or without signs and symptoms of congestive heart failure. Cardiotoxicity is usually reversible, even with continued trastuzumab therapy, using standard medication. Prior or concomitant anthracycline exposure was identified as a significant risk factor for cardiotoxicity in patients receiving trastuzumab.[15] However, a retrospective analysis has shown that the addition of trastuzumab to AC produces an overall survival benefit even when cardiac events are taken into account.[16] The combination of AC and trastuzumab has not been approved for use outside clinical trials, but studies exploring the use of trastuzumab with anthracyclines other than doxorubicin are ongoing.[17] Epirubicin is active in primary and metastatic breast cancer, with similar efficacy to doxorubicin but less cardiotoxicity.[18] The aim of the present phase II/III study was to evaluate the cardiac safety of trastuzumab plus epirubicin (Ellence)/cyclophosphamide (EC) in patients with HER2-positive disease and to compare it with that of EC alone in patients with HER2-negative breast cancer. Results of phase II of this study are presented here. **Methods Study Design**

This was a prospective, multicenter, open-label, phase II, parallel group, dose-escalation part of a
phase II/III study conducted in 25 centers in Germany. The primary objective was to evaluate the cardia safety of EC plus trastuzumab in women with HER2-positive MBC compared to that in women with HER2-negative MBC receiving EC alone. The secondary objective was to evaluate efficacy. During this dose-escalation part, 25 HER2-positive patients were scheduled to be recruited at dose level I (epirubicin at 60 mg/m$^2$, cyclophosphamide at 600 mg/m$^2$, trastuzumab at 2 mg/kg [EC60+H]). If cardiotoxicity was acceptable, the epirubicin dose would be escalated to dose level II (epirubicin 90 mg/m$^2$ [EC90+H]). Twenty-five patients would then be recruited to dose level II and 25 HER2-negative patients would be recruited to receive chemotherapy alone as a comparator group (EC90) with the same cardiotoxicity evaluation. The decision whether to escalate from EC60+H to EC90+H was based on the incidence of cardiotoxicity observed 3 weeks after the end of chemotherapy after six 3-week cycles of EC60 plus weekly trastuzumab. The primary safety parameter was cardiotoxicity according to predefined dose-limiting cardiotoxicity (DLC) criteria. These formed the basis for the decision rules for epirubicin dose escalation and study discontinuation. Dose-limiting cardiotoxicity was defined as an absolute decrease in LVEF of 10% points from the value at screening and to < 50%, clinical signs of congestive heart failure (New York Heart Association [NYHA] grades 1 to 4), severe arrhythmia requiring therapy, acute coronary syndrome or acute myocardial infarction requiring therapy, or the need for cardiopulmonary resuscitation. In the case of one cardiac event, the study could continue with escalation to EC90+H. If two or four cardiac events occurred, the Steering Committee was to decide whether to progress to dose level II. The occurrence of five or more cardiac events would lead to trial termination. After treating 25 patients each with six cycles of EC90 with or without trastuzumab, cardiac safety was again assessed 3 weeks after the end of chemotherapy and compared to the EC60+H arm. The steering committee would then base its recommendation for the phase III part of the study on the number of cardiac events seen with EC90+H. Dose level I would be used in the event of five or more cardiac events at dose level II, the steering committee would decide on which dose level to use in the event of two to four events, and one cardiac event would lead to full recruitment at dose level II (an additional 75 patients to both the EC90+H and EC90-alone groups, resulting in a total of 100 patients each).

**Patients**  
Women aged 18 to 70 years with MBC, an Eastern Cooperative Oncology Group (ECOG) performance status < 2, and life expectancy ≥ 3 months who had no prior anti-HER2 treatment, anthracycline therapy, or chemotherapy for MBC were eligible for study inclusion. For the trastuzumab-containing treatment arms, HER2 status needed to be immunohistochemistry (IHC) 3+ or fluorescence in situ hybridization (FISH)-positive. All patients gave written informed consent. Exclusion criteria included prior anti-HER2 treatment, cytotoxic chemotherapy for MBC, prior adjuvant anthracycline-containing chemotherapy or high-dose chemotherapy with peripheral stem cell transplantation, bone or central nervous system metastases as the only site of metastasis, history of other malignancy, serum creatinine > 1.5 * upper limit of normal (ULN), bilirubin > 1.5 * ULN, transaminases or alkaline phosphatase > 2.5 * ULN or > 5.0 * ULN in case of liver or bone metastases, serum calcium ≥ 12.0 mg/dL (3.0 mmol/L), pregnancy or lack of a reliable appropriate contraceptive method in women of childbearing potential, past participation in this study or in another study in the previous 4 weeks, or any condition likely to interfere with the conduct of the study. In addition, specific cardiovascular exclusion criteria included LVEF < 55% determined by two-dimensional (2D) echocardiography at rest, prior treatment with cardiotoxic agents, past or present coronary heart disease, valvular disease requiring treatment, cardiomyopathy or acute myocarditis, congestive heart failure, end-diastolic left ventricular diameter > 56 mm determined by M-mode echocardiography at rest, arrhythmias requiring treatment, poorly controlled arterial hypertension, or prior mediastinal irradiation.

**HER2 Testing**  
HER2 status was determined using archived primary tumor samples and a standard semiquantitative IHC test (DAKO HercepTest or FISH analysis (Vysis or Ventana). Inclusion of patients could be based on either local or central laboratory testing. Patients with tumors that were IHC 3+ and/or FISH-positive were eligible for the trastuzumab-containing treatment arms.  

**Treatment**  
On day 1, intravenous trastuzumab, epirubicin, and cyclophosphamide were administered according to standard prescribing information. Trastuzumab was administered as a 4-mg/kg loading dose followed by 2 mg/kg per week. No trastuzumab dose adjustment was permitted, but the drug was to be withheld in the event of grade 3 or 4 nonhematologic toxicity related to trastuzumab until recovery to grade 2 or better. In the event of recurrence of grade 3 or 4 nonhematologic toxicity, trastuzumab was to be discontinued. Trastuzumab treatment was continued in the presence of hematologic toxicity. Epirubicin/cyclophosphamide was administered every 3 weeks for six cycles at dose level I (epirubicin at 60 mg/m$^2$, cyclophosphamide at 600 mg/m$^2$) and for four to six cycles at dose level II (epirubicin at 90 mg/m$^2$, cyclophosphamide at 600 mg/m$^2$). Epirubicin was administered
intravenously over 30 minutes and followed by intravenous cyclophosphamide over 30 minutes. Patients received all cycles of chemotherapy at the same dosage. Treatment could be postponed for a maximum of 1 week only in the event of severe hematologic or nonhematologic toxicity. If there was no recovery from toxicity during this period, chemotherapy was to be discontinued. Palliative and supportive care for disease- and treatment-related symptoms were offered to all patients when indicated, and palliative radiotherapy was permitted if it did not compromise the evaluation of the indicator lesion. Any other drug other than antineoplastic drugs/agents and prophylactic dexrazoxane or prophylactic granulocyte colony-stimulating factor could be administered as concomitant medication.

**Assessment**

Cardiac function and adverse events were assessed using National Cancer Institute Common Toxicity Criteria at screening, weeks 1, 4, 7, 10, 13, and 16 during combination therapy, postchemotherapy at week 19, and for 12 weeks thereafter until week 103 or disease progression. Serious adverse events were reported immediately. Left ventricular ejection fraction was measured by 2D echocardiography, examinations were recorded on videotape, and the four-chamber view was used to assess ejection fraction (EF) in all patients. Ventricular volumes were measured by manual planimetry. The end-diastolic left ventricular (LV) volume was measured at the Q wave of the QRS complex. For the end-systolic LV volume, the smallest detectable volume was used. Calculation of EF was carried out using the following formula: EF = (end-diastolic LV volume - end-systolic LV volume)/end-diastolic LV volume. Serum cardiac marker concentrations (N-terminal brain natriuretic peptide and cardiac troponin-T) were measured over time to identify any correlation between changes of these markers and LVEF changes or symptoms of congestive heart failure. Response was assessed by bidimensional measurements every 6 weeks during the treatment period and every 12 weeks during follow-up using World Health Organization (WHO) criteria. Secondary efficacy parameters included time to progression and overall response rate defined according WHO criteria for progression and remission.

**Statistics**

The primary end point of this part of the study was to establish an anthracycline-containing combination regimen that is free of cardiotoxicity or associated with an acceptable rate of DLC using predefined criteria. The EC+H combination would be considered tolerable if the observed rate of DLC was < 10% and the number of patients was large enough to ensure that a true rate of ≥ 15% could be excluded statistically with 90% confidence. A cohort of patients treated with EC alone was included to estimate the difference in measurable LVEF changes between the two treatment regimens and the contribution of trastuzumab to DLC. To detect a difference in DLC of 5% (DLC with EC of about 5% vs ≤ 10% with EC+H) would require a very large sample size. For this reason, analysis is descriptive in nature. In the first stage, a cohort of 25 patients was selected on the basis that the dose level could be accepted as sufficiently tolerable if fewer than two cases of DLC were observed because the one-sided 90% confidence interval would be < 15%. In this instance, the decision to escalate to dose level II would be justified. If the same situation occurred at dose level II, 75 additional patients for each arm were to be included in the second stage of the study.

**Results**

**Patient Demographics**

A total of 26 patients were treated at dose level I with EC60+H. Twenty-five patients were then enrolled in the second cohort and treated at dose level II with EC90+H. Twenty-four patients with HER2-negative disease were recruited, one of whom was excluded due to violation of selection criteria. Patients’ baseline characteristics (age, ECOG performance status, stage of disease) were comparable in the three cohorts, apart from the differences in HER2 status as defined in the protocol. Exposure to study drugs was similar in all three cohorts (the median number of cycles of epirubicin and cyclophosphamide in all three cohorts was 6).

**Cardiac Safety**

Median LVEF at baseline in the EC60+H, EC90+H, and EC-alone cohorts was 70% (range: 57% to 82%), 71% (60% to 90%), and 70% (58% to 79%). Overall asymptomatic falls in LVEF of > 10% points during the whole observation period were detected in 12 out of 25 patients (48%) treated with EC60+H and in 14 out of 25 patients (56%) treated with EC90+H, vs 6 out of 23 patients (26%) in the EC90-alone cohort. Decreases of > 10% and to < 50% occurred only during treatment continuation with trastuzumab monotherapy. Eight cardiac adverse events that did not fulfill the protocol-defined criteria for cardiotoxicity were reported in five patients during treatment with EC60+H. These included arrhythmia (2 patients), atrioventricular block (1), hypokinesia (1), swelling of the lower limb (2), palpitations (1), and supraventricular tachycardia (1). In the EC90+H cohort, one cardiac event (transient absolute arrhythmia) was reported and considered related to trastuzumab, but the steering committee did not conclude that this fulfilled the protocol-defined criteria for DLC. Protocol-defined cardiotoxic events, with LVEF decreasing by > 10% to a value of < 50%, were experienced by three patients 5 to 6 months after the end of chemotherapy. The events...
were judged to be related to study treatment in all three women and are summarized as follows. A 61-year-old patient who had previously undergone adjuvant left-sided thoracic irradiation but had no cardiac history received six cycles of EC60+H. Her LVEF was 73% at baseline and 58% on completion of chemotherapy. Six months after completing chemotherapy, during treatment with trastuzumab alone, her LVEF decreased to 44% without symptoms of heart failure, and trastuzumab was stopped. Her LV dysfunction had not improved after 1 month. At this time, echocardiography revealed grade 1 mitral valve insufficiency, grade 2 tricuspid valve insufficiency, and a reduction in global LV function, plus mild pulmonary hypertension. At most recent follow-up, 8 months after diagnosis of these abnormalities, echocardiography showed normal global LV function, although the other abnormalities persisted. No therapeutic measures were taken in response to these events. A 57-year-old patient with a history of hypertension and peripheral edema was treated with six cycles of EC90+H. Her LVEF was 63% at baseline and 77% on completion of chemotherapy. Five months after completing chemotherapy, during treatment with trastuzumab alone, she presented with progressive dyspnea and orthopnea, and congestive heart failure was diagnosed (NYHA grade 3). Her LVEF was found to be 44% and echocardiography revealed pulmonary congestion, S3 gallop, tachycardia, hypokinesia, and mitral regurgitation. Trastuzumab therapy was stopped and she was treated with an angiotensin-converting enzyme inhibitor and diuretics. One month later, cardiac failure was reported to be improved but not resolved. Finally, a 64-year-old woman also completed treatment with EC90+H and continued to receive trastuzumab monotherapy. She had no history of cardiovascular disease and no cardiac risk factors at study entry, although she had received left-sided thoracic wall radiation. Her LVEF was 80% at baseline and 73% on completion of EC90+H. NYHA grade 2 congestive heart failure was diagnosed 6 months after completing chemotherapy, when her LVEF was 60%. No treatment was given and trastuzumab therapy was continued. LVEF was found to be 49% 3 months after the diagnosis of congestive heart failure. Trastuzumab was stopped and cardiovascular therapy consisting of hydrochlorothiazide, metoprolol, and symptom-adjusted ramipril (Altace) was started. The patient was diagnosed with pulmonary metastases at this time and withdrawn from the study due to disease progression. **Other Safety Data** The most common noncardiac and nonhematologic adverse events were alopecia, nausea, vomiting and arthralgia. Such events tended to occur at a similar incidence in all three patient groups, although a final assessment cannot be made actually due to the difference in duration of observation for the three patient groups. Stomatitis was observed only in patients receiving EC90+H (4 patients, 16%). Hematologic events were within the expected range and similar in all three groups. **Efficacy** After the completion of six cycles of treatment, the numbers of patients evaluable for efficacy in the EC60+H, EC90+H, and EC90-alone cohorts were 25, 25, and 23, respectively. One patient in the EC60+H cohort who withdrew prior to treatment due to leucopenia and malignant pleural effusion was considered as not responding. The overall response rates for EC60+H and EC90+H were > 60% (62% and 64%) vs 26% with EC90 alone. **Discussion** The interim results of this study have demonstrated that combination therapy with weekly trastuzumab plus 3-weekly EC did not produce an unacceptably high incidence of cardiotoxicity based on the protocoldefined criteria for this trial. In the two patients treated with EC90+H who experienced symptomatic congestive heart failure and the patient treated with EC60+H who experienced an asymptomatic decline in LVEF to < 50%, events that met the predefined criteria for DLC, the events occurred at least 5 months after cessation of chemotherapy, during treatment with trastuzumab alone. Cardiotoxicity was manageable and nonprogressive in all three cases. No patient treated with EC90 alone has experienced DLC to date. However, as fewer patients responded to EC90 alone than to EC+H, the majority of HER2-negative patients were lost to cardiac follow-up before the time when cardiac events were observed 4 to 6 months after the end of chemotherapy in the trastuzumab-containing study arm. All patients in this trial had close cardiac monitoring with LVEF assessments every 3 weeks during chemotherapy. Asymptomatic reductions in LVEF were observed in all three patient groups. However, changes were more pronounced in the trastuzumab-containing treatment arms. The clinical significance of these reductions is difficult to assess because intrapatient variations in LVEF over time were common and the open-label study design probably led to observation bias. However, this study demonstrates that asymptomatic reductions in LVEF do not always progress to congestive heart failure in patients with MBC, and that congestive heart failure may not be preceded by an asymptomatic reduction in LVEF, as was observed in one patient in this study. The observation of cardiotoxicity in this trial was not unexpected, as a retrospective review of available data from 1,219 patients in seven clinical trials has indicated that the incidence of cardiotoxicity is increased when trastuzumab is combined with anthracyclines, which are also associated with cardiotoxicity.[15,19] The interim efficacy results for treatment with trastuzumab plus EC are
promising. The response rates for EC60+H and EC90+H, at 62% and 64%, are similar to those reported for patients treated with trastuzumab plus AC (predominantly doxorubicin), which was superior to the best available standard chemotherapy.[14] This raised the question whether the study should proceed with only one dose level as initially planned. In contrast, preliminary data for the control group appear to indicate that the response to EC alone in patients with HER2-negative disease (26%) is inferior to the trastuzumab-containing regimen in patients with HER2-positive disease. This interesting observation may be due to a higher rate of hormone-receptor-positive patients in the EC-alone arm with a presumed higher response to endocrine therapy vs chemotherapy. This needs to be confirmed by evaluation of a larger group of patients, which is planned in the expanded phase of this trial. It may be possible that HER2 status influences the outcome of anthracycline therapy, with HER2-positive tumors responding better to anthracyclines than HER2-negative tumors.[9,20]

Conclusion

In conclusion, combination therapy with trastuzumab plus an anthracycline and cyclophosphamide is highly effective in the treatment of metastatic breast cancer and warrants further study. The interim results of this study indicate that it is feasible to combine trastuzumab with the less cardiotoxic anthracycline epirubicin, without the high risk of cardiotoxicity seen during treatment with trastuzumab plus doxorubicin. However, LVEF measurements were very variable. Central review of echocardiograms has been incorporated into the next stage of the trial to improve the consistency of LVEF evaluation. The finding that treatment with an epirubicin-containing regimen leads to asymptomatic decreases in LVEF resulted in the primary end point for the phase III study being revised to focus on symptomatic events, which appear to occur 4 to 6 months after the end of chemotherapy. For this reason, all patients will be followed for 2 years regardless of response to study treatment. The combination of trastuzumab plus EC has shown promising efficacy, regardless of epirubicin dose. Based on this, the trial will be expanded to investigate further the safety and efficacy of this combination. Discussions with the steering committee and an international oncology advisory board led to the decision to continue with both trastuzumab-containing treatment arms (EC60+H and EC90+H) and a comparator arm of EC90 alone.

Disclosures:

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