Phase II Feasibility and Pharmacokinetic Study of Concurrent Administration of Trastuzumab and High-Dose Chemotherapy in Advanced HER2+ Breast Cancer

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ABSTRACT

Purpose: To evaluate the safety of concurrent treatment with trastuzumab and high-dose chemotherapy (HDC), using cyclophosphamide, cisplatin, and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), with autologous hematopoietic progenitor cell support, in patients with HER2+ advanced breast cancer.

Experimental Design: Patients with HER2-overexpressing high-risk primary breast cancer (HRPBC; defined as ≥4 involved nodes or inflammatory disease), or metastatic breast cancer (MBC) were eligible. Treatment consisted of a loading dose of trastuzumab at 4 mg/kg (day −5), HDC (days −5 to −2), autologous hematopoietic progenitor cells infusion on day 0, and weekly maintenance trastuzumab (2 mg/kg) from day +1 (minimum of 9 doses). Cardiac monitoring included serial left ventricular ejection fraction measurements before treatment and on days +20 and +65.

Results: Thirty-three patients were prospectively enrolled (13 HRPBC, 20 MBC). Toxicity seemed similar to that expected with this HDC regimen alone. Neutrophils and platelets engrafted promptly. There were no cases of grade 4 or 5 toxicity. One patient experienced symptomatic grade 3 acute cardiac failure on day −4, responsive to treatment.

Trastuzumab did not alter the pharmacokinetics of HDC. Eleven of twelve MBC patients with measurable disease (nine of them refractory to previous chemotherapy) experienced an objective response (9 complete and 2 partial responses). At median follow-up of 34 (13–58) months, all HRPBC patients remain alive and free of disease; the MBC group has event-free survival and overall survival rates of 45 and 70%, respectively.

Conclusions: Incorporation of trastuzumab into HDC (cyclophosphamide, cisplatin, and BCNU) is feasible, with no apparent increased toxicity or pharmacokinetic interactions.

INTRODUCTION

Overexpression of the HER2 oncogene, which occurs in 20 to 30% of invasive breast cancers, is associated with decreased survival (1). The monoclonal antibody trastuzumab, directed against the HER2 protein on the surface of the breast cancer cell, induces a response in 10 to 15% of metastatic breast cancer (MBC) patients treated previously (2, 3) and up to 26% when used as first-line therapy (4).

Preclinical studies have shown synergy between trastuzumab and a number of chemotherapeutic agents, including alkylators, such as cyclophosphamide or thiota, platinum compounds, or microtubule-acting drugs, such as docetaxel or vinorelbine (5). Pegram et al. (6) observed a 24% response rate with concurrent cisplatin and trastuzumab, administered for 9 doses, in patients with refractory MBC, a scenario in which cisplatin alone is considered to have minimal activity. Subsequently, the addition of trastuzumab to either doxorubicin-cyclophosphamide or to paclitaxel improved survival by 25% in a randomized phase III trial of first-line treatment for MBC (7).

The use of high-dose chemotherapy (HDC) with autologous hematopoietic progenitor cells support has been compared with standard-dose chemotherapy in high-risk primary breast cancer (HRPBC), defined as extensive axillary involvement or inflammatory carcinoma or MBC (reviewed in ref. 8). Overall, their results, in many cases preliminary, cannot be considered conclusive at this point. In HRPBC, there are negative trials after fairly mature follow-up (9–12). In contrast, other studies have shown a nonsignificant trend in favor of transplant (13–15), or significant superiority of transplant at the time of their first analysis (16, 17). In MBC, whereas some trials (including the only one that has undergone final analysis and publication) have failed to show any differences (18, 19), several others (published only as abstracts) have suggested an advantage in event-free survival (EFS) in favor of HDC (20–25). However, in only one of all those MBC studies has a resulting overall survival benefit been observed to date (19). Thus, whereas
longer follow-up of the randomized trials and meta-analyses of their pooled data are needed, HDC cannot, at present, be considered standard treatment of any breast cancer population.

Independent of the question of whether or not HDC, as administered in the randomized trials, is superior to standard therapy, novel strategies combining HDC with molecularly targeted agents may improve patient outcome. We and others have identified overexpression of HER2 as an independent adverse predictor after HDC, both in HRPBC (26–29) and MBC (30–33). Furthermore, Rodenhuis et al. (13) of the National Dutch trial, the largest randomized study of HDC in HRPBC, have reported an unplanned subset analysis based on HER2 status, suggesting a differential benefit of HDC in patients with HER2-tumors compared with those with HER2+ disease. We aimed to overcome the resistance to HDC resulting from HER2 overexpression through concurrent administration of trastuzumab with alkylator-based HDC, in an attempt to maximally exploit their synergy. Because concomitant administration of trastuzumab with standard chemotherapy can cause increased cardiac side effects (34), cardiotoxicity could limit concurrent treatment with trastuzumab and HDC.

We previously analyzed the incidence of cardiotoxicity in 443 patients after high-dose cyclophosphamide, cisplatin, and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) (CCB or STAMP-I; ref. 35). Most patients experienced a small and asymptomatic drop of the left ventricular ejection fraction (LVEF) after transplant, with a relatively low (5.1%) incidence of symptomatic cardiomyopathy, which suggested to us that this might be a potentially useful regimen to combine with trastuzumab. We report here a prospective evaluation of the feasibility and pharmacokinetics of concurrent administration of trastuzumab with CCB.

PATIENTS AND METHODS

Patient Population. This study was open to accrual at the Universities of Colorado and Duke between 1999 and 2003. Patients prospectively enrolled had HER2-positive histologically proven breast cancer, either high-risk stage II-III (defined as ≥4 involved axillary nodes or inflammatory carcinoma) or stage IV disease. At the start of the study, we defined HER2 positivity as 2+ or 3+ by immunohistochemistry. In 2001, the protocol was amended to define HER2 positivity as 3+ by immunohistochemistry or positive by fluorescence in situ hybridization, with all 2+ immunohistochemistry cases requiring confirmation by fluorescence in situ hybridization. The clinical research protocol was approved by the Comprehensive Cancer Center Protocol Review Committees and Institutional Review Boards at Colorado and Duke. An external Data Safety Monitoring Board reviewed the study data every 6 months. All patients gave written informed consent before study entry.

Patient evaluation included computed tomography scans of the head, chest, abdomen and pelvis, bone scan, bilateral iliac crest bone marrow biopsies, and visceral organ function testing with pulmonary function tests, radionuclide ventriculogram, and measurement of serum creatinine, bilirubin, aspartate aminotransferase and alanine aminotransferase. Enrollment criteria required proof of HER2 overexpression and adequate visceral organ function, defined as follows: forced expiratory volume in one second >60% of predicted, carbon monoxide diffusion capacity for the lung >60% of predicted, LVEF (measured by radionuclide ventriculogram) >45% at rest and with at least 5% augmentation on exercise, creatinine clearance (measured or estimated with the Cockcroft-Gault formula) ≥60 mL/minutes, and bilirubin/aspartate aminotransferase/alanine aminotransferase <1.5 times the upper limit of normal values.

Cumulative anthracycline exposure was limited to 400 mg/m² doxorubicin, 600 mg/m² epirubicin, or 100 mg/m² mitoxantrone, before HDC. Prior exposure to trastuzumab was allowed.

Treatment Administered. Patients were admitted on day −6, at which time intravenous hydration sufficient to ensure a urinary output >200 mL/hour and continuous bladder irrigation were initiated (Table 2). All chemotherapy drug doses were calculated based on the actual patient body surface area, unless the actual weight was ≥20% over the ideal body weight, in which case the average of the actual and the ideal weight was used to calculate the body surface area. Cisplatin was administered at 165 mg/m² as a 72-hour intravenous continuous infusion, starting on day −5. Cyclophosphamide was delivered at 1,875 mg/m²/day as a 1-hour intravenous infusion, on days −5, −4 and −3. A 5-day regimen of mitoxantrone, before HDC. Prior exposure to trastuzumab was allowed.

Trastuzumab was administered at 4 mg/kg intravenously on day −5, before initiation of cyclophosphamide and cisplatin, and continued, from day +1, at 2 mg/kg intravenously every week. In its original design, the protocol specified 9 doses of trastuzumab, following the available data at that time from the study by Pegram et al. (6) of trastuzumab plus cisplatin. The protocol was amended in 2000 to allow more prolonged durations of treatment for patients with metastatic disease, at the discretion of the treating oncologist. The study protocol required discontinuation of trastuzumab if LVEF on day +20 was <50% or in the presence of cardiac-related symptoms. Trastuzumab was allowed during post-HDC radiotherapy, either to locoregional or to metastatic sites. Post-transplant first- or second-line hormonal treatment, with tamoxifen or an aromatase inhibitor, was prescribed for 5 years to patients with hormone receptor-positive tumors.

Autologous hematopoietic progenitor cells were infused on day 0. Uniform supportive care measures were used as described previously. Prochlorperazine, diphenhydramine, and lorzepam were used as antiemetic therapy. Levofloxacin was administered beginning on day −2, for infection prophylaxis. Patients with febrile neutropenia were switched to cefepime and vancomycin. Antifungal treatment was added for patients who remained febrile 48 to 96 hours after starting empiric antibiotics. Patients received packed red blood cell transfusions for a hematocrit <28% and single donor apheresed platelets for platelet count <10,000/μL. All blood products were irradiated. Patients in stable condition were discharged on day −1 to be followed daily as outpatients until engraftment. Post-transplant granulocyte colony-stimulating factor was administered at 5 μg/kg/day, from day 0 until neutrophil engraftment.

Time to engraftment was defined as the number of days after transplant to achieve an absolute neutrophil count of ≥500/ mm³ and an unsupported platelet count of ≥20,000/mm³. Tox-
Concurrent Trastuzumab and High-Dose Chemotherapy

Pharmacokinetic Studies. Patients had pharmacokinetic (PK) analysis of cyclophosphamide, cisplatin, and BCNU. Blood sampling, assay methodology, and analysis were done as described previously (37).

End-Points of the Study and Statistical Considerations.
The goal of this study was to evaluate the feasibility of concurrent combination of trastuzumab with HDC. Therefore, toxic death rate and incidence of grade 3 to 4 regimen-related toxicity, particularly cardiotoxicity, were the primary end-points.

The minimum accrual was prospectively established as 30 patients, with built-in stopping rules for cardiotoxicity and treatment-related mortality. The two-stage stopping rules for cardiotoxicity that the protocol contemplated were as follows: 15 patients were to be enrolled in the first stage of the trial. If four or more patients experienced grade 3 to 4 cardiotoxicity, the trial was to be stopped concluding that the severe cardiotoxicity rate exceeds 5%. If three or fewer patients experienced this toxicity, 15 additional patients were to be enrolled. If the cumulative number of grade 3 to 4 cardiotoxic events was four or more, the trial was to terminate concluding that the severe cardiotoxicity rate exceeds 5%. This two-stage design had 86% power to detect >5% grade 3 to 4 cardiotoxicity rate with a type I error rate of 5.8% (38).

The stopping rule for toxic deaths assumed a HDC-related mortality rate <5%. We believed that a toxic death rate in excess of 5% would not be acceptable. On the basis of this assumption and a population binomial parameter for toxicity of 0.05, the trial was to be stopped at any point that the number of toxic deaths reached or exceeded three.

The exact binomial distribution was used to estimate the 95% confidence interval of the incidence of cardiotoxicity was estimated. Survival analyses used the Kaplan-Meier method (39). EFS was defined as the time from study entry to a documented relapse or progression, or death without relapse or progression. Overall survival was defined as the time from study entry to death from any cause.

Secondary endpoints of this study were to evaluate potential PK interactions between trastuzumab and cyclophosphamide, cisplatin, or BCNU, as well as to describe the outcome of enrolled patients. We compared the pharmacokinetic parameters of patients enrolled in this study with those in our database who received STAMP-I without trastuzumab using the Kruskal-Wallis test. The SAS software package, version 6.12 (SAS Institute Inc., Cary, NC) was used to perform all statistical calculations.

RESULTS

Patient Enrollment. From September 1999 to November 2003, 33 patients were prospectively enrolled on this study (Table 1). Thirteen patients had high-risk stage II-III disease, six of them inflammatory carcinoma. Eight of these patients had a high pretransplant predictive score (poor risk; ref. 40). Twenty patients had MBC, most of them with widespread metastases refractory to previous chemotherapy.

High-Dose Treatment. Thirty-two patients completed HDC as described above (Table 2). One patient had HDC discontinued on day −4 after two doses of cyclophosphamide, because of acute grade 3 cardiac toxicity (described in the section below). Overall, no patients experienced grade 4 or 5 icacies were graded following the National Cancer Institute Common Terminology Criteria for Serious Adverse Events, version 3.0 (36).

**Table 1** Patient demographics (N = 33)

<table>
<thead>
<tr>
<th>Age, median (range)</th>
<th>46 (29–59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 IHC grading</td>
<td></td>
</tr>
<tr>
<td>2+ (FISH +)</td>
<td>7</td>
</tr>
<tr>
<td>3+</td>
<td>26</td>
</tr>
<tr>
<td>Hormone receptors</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>17</td>
</tr>
<tr>
<td>Negative</td>
<td>16</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>IIB-IIIC</td>
<td>13</td>
</tr>
<tr>
<td>Predictive score a</td>
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</tr>
<tr>
<td>High</td>
<td>8</td>
</tr>
<tr>
<td>Low</td>
<td>5</td>
</tr>
<tr>
<td>IBC</td>
<td>6</td>
</tr>
<tr>
<td>No. positive nodes: median (range)</td>
<td>16 (4–26)</td>
</tr>
<tr>
<td>IV</td>
<td>20</td>
</tr>
<tr>
<td>No. sites</td>
<td></td>
</tr>
<tr>
<td>Multiple metastases</td>
<td>16</td>
</tr>
<tr>
<td>Oligometastatic</td>
<td>4</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
</tr>
<tr>
<td>Chemorefractory</td>
<td>11</td>
</tr>
<tr>
<td>Chemosensitive</td>
<td>1</td>
</tr>
<tr>
<td>Not evaluable (bone disease)</td>
<td>8</td>
</tr>
<tr>
<td>Organ involvement</td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>10</td>
</tr>
<tr>
<td>Liver</td>
<td>6</td>
</tr>
<tr>
<td>Lungs</td>
<td>7</td>
</tr>
<tr>
<td>Pleura</td>
<td>3</td>
</tr>
<tr>
<td>Bone</td>
<td>8</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>8</td>
</tr>
<tr>
<td>Skin/chest wall</td>
<td>4</td>
</tr>
<tr>
<td>Prior therapy</td>
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<tr>
<td>No. prior chemotherapy regimens: median (range)</td>
<td>2 (1–6)</td>
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<tr>
<td>Prior doxorubicin</td>
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</tr>
<tr>
<td>Median cumulative dose (range)</td>
<td>240 (180–360) mg/m²</td>
</tr>
<tr>
<td>Prior taxanes</td>
<td>27</td>
</tr>
<tr>
<td>Prior trastuzumab</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: FISH, fluorescence in situ hybridization; ER, estrogen receptors; PR, progesterone receptors.

*a Score 40 = (nodal ratio × 3.05) + (tumor size × 0.15) − ER/PR × 1.1. High (≥2.41) score: high (60%) relapse risk. Low (<2.41) score: low (15%) relapse risk.

**Table 2** Treatment schema

<table>
<thead>
<tr>
<th>Days</th>
<th>Trastuzumab 4 mg/kg IV</th>
<th>Cyclophosphamide</th>
<th>Cisplatin 55 mg/m²/day, 72-hour CI</th>
<th>BCNU 600 mg/m²</th>
<th>Trastuzumab 2 mg/kg intravenously/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>−5</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−4</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−3</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−2</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>1</td>
<td>✓</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
toxicities. Sixteen patients (48%) developed grade 2 interstitial pneumonitis, which resolved in all cases after steroid treatment, as described previously (41). There was one case each of grade 2 and grade 3 acute renal failure, grade 3 encephalopathy with dizziness and mental status changes, and grade 3 hearing loss. No severe infectious complications were noticed. Neutrophil engraftment occurred on median day +9 (range, +8 to +11). Platelets engrafted on median day +12 (+9 to +37).

**Cardiac Toxicities.** The combined trastuzumab-HDC regimen was well tolerated from a cardiac standpoint. There was one case of symptomatic cardiac toxicity (3% incidence, 95% confidence interval, 0–15.8%). This was a 36-year-old patient with a right-side locally advanced breast cancer unresponsive to six cycles of doxorubicin-docetaxel, with subsequent invasion of the chest wall and pleural space. Her cumulative doxorubicin dose was 300 mg/m², and her pretransplant cardiac function was normal with an LVEF of 64%. Shortly after HDC start, she developed grade 3 acute heart failure, which prompted discontinuation of HDC on day –4, after administration of the loading dose of trastuzumab, 2 doses of cyclophosphamide, and a 1-day infusion of cisplatin. An echocardiogram showed diastolic dysfunction of the left ventricle with apical akinesis and depressed LVEF of 30%. The patient’s condition improved rapidly on diuretics, captopril and digoxin. On day +20, with her cardiac medications discontinued, the patient’s LVEF had recovered to 60%. She remained asymptomatic and stable from a cardiac standpoint, with a repeat LVEF on day +65 of 55%.

No other patients experienced symptomatic cardiac complications. After the protocol, trastuzumab was discontinued after day +20 in two patients because of asymptomatic LVEF drops to 32 and 38%, respectively. Their LVEF recovered to 51 and 53%, respectively, on day +65.

Median pre-HDC LVEF was 60% (range, 48–77%). At days +20 and +65, those values were 52% (32 to 72%), and 56% (40–73%; Fig. 1). The LVEF dropped significantly between the pre-HDC evaluation and day +20 ($P = 0.001$), but not between the pre-HDC evaluation and day +65 ($P = 0.15$). When comparing the results of serial cardiac monitoring in this study to those of 163 breast cancer patients who had previously received cyclophosphamide, cisplatin, and BCNU at our institution (19), there were no significant differences in pre-HDC LVEF ($P = 0.6$), day +20 LVEF ($P = 0.5$), or in LVEF change, expressed as absolute value ($P = 0.3$) or percentage of pre-HDC result ($P = 0.25$; Table 3).

**Trastuzumab Therapy.** No serious infusion-related reactions were observed. Thirty-two patients started maintenance weekly of trastuzumab at 2 mg/kg intravenously on day +1. The patient who developed acute grade 3 cardiac toxicity during HDC did not receive any further trastuzumab. Trastuzumab was discontinued, after 3 maintenance doses, in two patients whose day +20 LVEF had dropped to <40%. Their day +65 LVEF measurements recovered to 53 and 51%, respectively. The remaining 29 patients received a median 9 (9–48) maintenance doses of trastuzumab. Eleven of the 20 MBC patients continued trastuzumab after the 9th dose, for a median 25 (15–48) doses.

**Local Treatment.** Upon platelet recovery, all 13 HR-PBC patients and nine MBC patients received radiotherapy to locoregional and metastatic sites, respectively. Of them, seven HRPBC and six MBC patients had radiotherapy postponed until after completion of the 9 maintenance doses of trastuzumab. Six HRPBC (four of them on the left breast tumors) and three MBC patients received trastuzumab throughout radiotherapy. None of the 22 patients experienced any substantial side effects from radiotherapy, including the nine patients who received it concurrently with trastuzumab.

**Activity and Outcome.** Among 12 MBC patients with measurable lesions (nine of them with chemorefractory disease), there were 9 complete responses and 2 partial responses. The

**Table 3.** LVEF changes (pre-HDC to day +20)

<table>
<thead>
<tr>
<th></th>
<th>Pre-HDC LVEF: mean (SD) %</th>
<th>$P$ value</th>
<th>Absolute LVEF drop: mean (SD) %</th>
<th>$P$ value</th>
<th>LVEF drop (% baseline): mean (SD)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCB (N = 163)</td>
<td>61 (6.4)</td>
<td>0.4</td>
<td>5.1 (7.4)</td>
<td>0.24</td>
<td>6.2 (12)</td>
<td>0.18</td>
</tr>
<tr>
<td>H-CCB (N = 33)</td>
<td>60 (6.4)</td>
<td>$P$</td>
<td>6.3 (8.3)</td>
<td>$P$</td>
<td>9.6 (12.7)</td>
<td>$P$</td>
</tr>
</tbody>
</table>

NOTE. Comparison with historical dataset treated with CCB alone.
nonresponding patient was the one who had HDC discontinued prematurely. At overall median follow-up of 34 (13–58) months, all HRPBC patients were alive and free of disease. Among the MBC group, the EFS and overall survival rates were 45 and 70%, respectively, with median EFS time of 16 months, and median overall survival not reached yet (Fig. 2A and B).

**PK Analyses.** PK analyses of cyclophosphamide, cisplatin, and BCNU were done in 24 patients. We found no significant differences between the area under the curve values of all three drugs compared with those from 476 patients who had previously received CCB without concurrent trastuzumab at Colorado, using the same laboratory assays in all cases (Table 4).

**DISCUSSION**

We prospectively evaluated the concurrent administration of trastuzumab with HDC (CCB) in patients with HER2+ advanced breast cancer. The use of concurrent treatment with trastuzumab and CCB did not result in increased toxicities compared with those expected with CCB alone. No grade 4 or 5 toxicities were observed, which made this therapy acceptable by common autologous transplantation standards.

Similar to that observed with CCB alone (35), there was an asymptomatic drop in LVEF from before to after transplant in most patients, recovering to normal values by day +65. The 3% incidence of symptomatic grade 3 or greater cardiotoxicity seems similar to our prior experience using CCB. Although these observations are encouraging, confirmation of the level of safety we observed in this study would be desirable.

Cardiotoxicity after trastuzumab in monotherapy has been reported in 3 to 7% of patients (34). Likewise, an increased incidence of cardiac toxicity has been observed with combinations of trastuzumab and chemotherapy, with congestive failure rates of 27% after doxorubicin/cyclophosphamide combined with trastuzumab (versus 8% without trastuzumab), and 13% after trastuzumab-paclitaxel (versus 1% with paclitaxel alone; ref. 34). Some observations suggest that HER2 may be a survival factor for myocytes (42, 43) and that cardiac myocyte injury mediated by this receptor causes the cardiomyopathy associated with trastuzumab. However, the mechanisms of trastuzumab-related cardiotoxicity remain unclear (44).

When this study was designed, 9 maintenance doses of trastuzumab were specified, following the pioneering trial by Pegram et al. (6) of trastuzumab plus cisplatin. In subsequent years, prolonged maintenance trastuzumab was shown to be feasible and gained favor in the management of HER2+ MBC patients (3, 4), and our protocol was amended accordingly. No

**Table 4** Comparison of the area under the curve (μg · ml⁻¹ · min⁻¹), expressed as median (range), of cyclophosphamide, cisplatin, and BCNU, of patients who received trastuzumab-CCB and historical dataset treated with CCB alone

<table>
<thead>
<tr>
<th></th>
<th>Cyclophosphamide</th>
<th>Cisplatin</th>
<th>BCNU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab-CCB</td>
<td>70,200 (25,100–112,600)</td>
<td>540 (370–910)</td>
<td>530 (260–850)</td>
</tr>
<tr>
<td>CCB (N = 476)</td>
<td>75,900 (28,700–148,900)</td>
<td>530 (280–1,560)</td>
<td>480 (90–3,260)</td>
</tr>
<tr>
<td>P value</td>
<td>0.5</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Fig. 2 Kaplan-Meier EFS (Fig. 2A) and overall survival (Fig. 2B) curves.
late cardiac complications were observed among the eleven MBC patients in our study who received prolonged maintenance therapy. Although our study was not designed to evaluate prolonged maintenance trastuzumab after HDC, the observed recovery of LVEF by day +65 (i.e., around the time patients continued maintenance trastuzumab beyond the 9th dose) suggests that cardiac tolerance might be similar to that expected in patients without prior HDC.

Concurrent trastuzumab-radiotherapy was authorized in our study for cases where the investigators considered that delaying radiotherapy until the end of maintenance trastuzumab treatment could represent a high risk of tumor growth. It was not our goal to test the feasibility of this concurrent approach, and no conclusions can be drawn from our limited experience. It is possible that radiotherapy, particularly to the left chest, might increase the potential cardiotoxicity of trastuzumab, or that the antibody may potentiate radiotherapy-induced skin or soft tissue toxicity. Although the concurrent use of trastuzumab and radiotherapy is supported by preclinical evidence of synergy (45), this approach should be prospectively evaluated in specifically designed studies.

Pharmacokinetic interactions with HDC are common, particularly involving drugs metabolized via P-450 microsomal isozymes, such as cyclophosphamide or BCNU, or drugs excreted renally, such as cisplatin. However, there is no evidence that trastuzumab is metabolized by the P-450 enzyme system or is excreted renally. The results of our study show that pharmacokinetics of cyclophosphamide, cisplatin, and BCNU, administered at high doses, are not altered in the presence of trastuzumab. Previous reports indicated that the pharmacokinetics of trastuzumab are not affected by the presence of chemotherapy drugs (46, 47).

Efforts at overcoming drug resistance to HDC through modulation of its antitumor activity have been hampered by the broad lack of selectivity of the sensitizing compounds, which can decrease the therapeutic index of HDC through increased toxicity on normal tissues. Many drug resistance mechanisms, such as membrane transport, thiol scavenging, and DNA repair, are common to malignant and normal cells. Elias et al. (48) reported excessive toxicity resulting from concurrent administration of etanidazole, a hypoxic cell sensitizer (which, theoretically, would confer an advantage to normal, well-oxygenated tissues) and HDC, using ifosfamide, carboplatin, and etoposide. Other compounds, capable of reversing chemotherapy resistance in preclinical models, such as novobiocin (49) or lomidamine (50), have not caused a substantial increase of the antitumor activity of HDC when tested clinically.

A more selective way of modulating the effect of HDC may be that mediated by receptor-binding of monoclonal antibodies. Preliminary results suggest the feasibility of concurrent administration of HDC with anti-CD20 monoclonal antibody rituximab (51–53), or radiolabeled antibodies $^{131}I$-tositumomab (54), or $^{90}$yttrium-ibritumomab (55, 56) in patients with non-Hodgkin’s lymphoma. HER2 is overexpressed in selected breast tumors compared with other tissues. The antibody evaluated in the present study, trastuzumab, has been shown to inhibit the tumor cell mechanisms of repair of cisplatin-induced DNA damage (57, 58) and presents synergy with a number of chemotherapeutic agents. Although this study was not designed to evaluate the activity or efficacy of this approach, it should be noted that patients enrolled in this study represented a very poor prognosis group. Most of the HRPBC patients had a high prognostic score (40), which predicts >50% risk of relapse after HDC within 3 years, and the majority of MBC patients had widespread chemorefractory tumors. Thus, our preliminary observations suggesting a high level of activity are noteworthy and would merit further study in an expanded patient population.

In conclusion, our study shows that concurrent administration of trastuzumab and HDC with CCB is feasible and causes no undesired PK interactions, with preliminary observations of excellent activity in patients with poor prognosis breast cancer. On the basis of these results, future research on concurrent treatment with trastuzumab and newer, more breast cancer-specific HDC regimens, holds promise.

REFERENCES

Concurrent Trastuzumab and High-Dose Chemotherapy


Clinical Cancer Research

Phase II Feasibility and Pharmacokinetic Study of Concurrent Administration of Trastuzumab and High-Dose Chemotherapy in Advanced HER2+ Breast Cancer


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