A Pilot Study of Dose-Dense Paclitaxel With Trastuzumab and Lapatinib for Node-negative HER2-Overexpressed Breast Cancer

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Abstract

Treatment of human epidermal growth factor receptor-2 (HER2)-positive breast cancer with dual anti-HER2 therapy has been shown to improve outcomes. In the present pilot phase II study, patients with early-stage HER2-positive breast cancer received adjuvant treatment with dose-dense paclitaxel, trastuzumab, and lapatinib. However, this combination was not feasible because of unexpected toxicity.

Background: Dual anti-HER2 therapy is effective for HER2-amplified breast cancer. Weekly paclitaxel, trastuzumab, and full-dose lapatinib (PTL) is not feasible because of grade 3 diarrhea. We conducted a phase II feasibility study of dose-dense (DD; every other week) PTL (ClinicalTrials.gov identifier, NCT01827163). **Patients and Methods:** Eligible patients had HER2-positive breast cancer, tumor size $\leq$ 3 cm, and negative nodes. Treatment included paclitaxel (175 mg/m^2 $\times$ 4, every 2 weeks with pegfilgrastim), trastuzumab (4 mg/kg load and then 2 mg/kg weekly), and lapatinib (1000 mg daily). After paclitaxel $\times$ 4, trastuzumab (6 mg/kg every 3 weeks) plus lapatinib were continued for 1 year. The primary endpoint was feasibility, defined as (1) $>$ 80% of patients completing PTL without a dose delay or reduction, (2) grade 3 diarrhea rate $<$ 20%, and (3) cardiac event rate $<$ 4%. **Results:** From May 2013 to November 2013, we enrolled 20 of 55 planned patients. The median age was 49 years (range, 34-74 years). One patient had immediate paclitaxel hypersensitivity and was deemed inevaluable. Only 13 of 19 evaluable patients (68%) completed PTL without a dose delay or reduction or unacceptable toxicities. Only 3 of 19 (16%) had grade 3 diarrhea. Rash was frequent, with all grades in 18 of 19 (95%) and grade 3 in 2 of 19 (11%). The study was stopped early because of excess toxicity. **Conclusion:** The discontinuation rate during DD PTL was high, owing, in part, to an unexpectedly high incidence of rash. The trial was halted, because the initial discontinuation rate from overall toxicity made it unlikely that full accrual would demonstrate feasibility.

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Introduction

We previously conducted a trial of dose-dense (DD) doxorubicin and cyclophosphamide (AC) followed by weekly paclitaxel with trastuzumab and lapatinib (PTL) in patients with stage I to III breast cancer with overexpression or amplification of the human epidermal growth factor receptor-2 (HER2) and reported that this combination was not feasible owing to a high rate of grade 3 diarrhea.[1] Specifically, this regimen was not feasible with a lapatinib dose of 1000 mg daily, because all-grade diarrhea was experienced by 88% of patients, with 29% of these patients experiencing grade 3 diarrhea. The study was closed early, because 43% of patients required a lapatinib dose reduction owing to grade 3 or unacceptable grade $\leq$ 2 diarrhea. These findings established key safety data and led to the modification of the PTL arm of the larger phase III

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adjuvant study, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO). Other studies have demonstrated similarly high rates of diarrhea with PTL at a lapatinib dose of 1000 mg daily.[2-4] Additionally, diarrhea was reported to be the dose-limiting toxicity for this combination when administered in the metastatic setting.[5]

Dual targeting of HER2 has been demonstrated to be superior to single-agent anti-HER2 therapy in both the metastatic and the neoadjuvant settings.[2,3,6-8] The ALTTO study randomized patients to single-agent trastuzumab with taxane versus taxane plus dual anti-HER2 therapy with trastuzumab and lapatinib at a modified dose of 750 mg during the taxane phase. In a pooled analysis of lapatinib usage in the metastatic setting, Crown et al[9] reported a low incidence of grade 3 diarrhea (< 10%) when lapatinib was combined with paclitaxel administered every 3 weeks at various doses. Both the every-3-week and DD (every-2-week) schedules of paclitaxel administration were associated with a low incidence of diarrhea.[10] We hypothesized that the optimally tolerated dose of lapatinib 1000 mg daily with trastuzumab could be administered with DD paclitaxel.[11] To identify alternate, tolerable dual anti-HER2 regimens in the adjuvant treatment of breast cancer, we conducted a phase II study of trastuzumab plus lapatinib at the full dose of 1000 mg with DD paclitaxel.

Patients and Methods

The present study was a phase II trial of adjuvant chemotherapy with DD paclitaxel with trastuzumab and lapatinib. Patients received endocrine therapy and radiation, as appropriate. The primary objective was to determine the feasibility of this regimen in patients with lymph node-negative HER2-overexpressed/amplified breast cancer with a primary tumor size of ≤ 3 cm. Feasibility was defined as completion of the PTL portion of the regimen without a dose delay or reduction or grade ≥ 3 QTc prolongation. Given that $> 85\%$ of patients enrolled on standard adjuvant trials complete the intended study regimens without a dose delay or reduction,[10,12-14] we planned to accrue 55 patients to our study. With this sample size, we would have had 90% power and 5% type I error to discriminate between true completion rates of $\leq 65\%$ and $\geq 80\%$. A completion rate of $\leq 65\%$ would indicate that this regimen was not feasible. Thus, the regimen would be considered feasible if ≥ 42 patients completed the DD PTL portion without a dose delay or reduction.

With regard to safety, we incorporated 2 early termination rules for gastrointestinal and cardiac toxicity. The allowable rate of grade 3 diarrhea was set at 20%, and the unacceptable rate was set at 40%. Assessment of the diarrhea rate was preplanned after enrollment of every 10th patient based on repeat significance testing. The probability of stopping the trial for a true diarrhea rate of 20% and 40% was 12% and 97%, respectively. With regard to the second stopping rule, the allowable incidence of cardiac events was set at $\leq 4\%$, a rate consistent with reported adjuvant trastuzumab trials.[15-17] A cardiac event was defined as (1) cardiac death or (2) symptomatic congestive heart failure (CHF) defined as dyspnea with normal activity or at rest and an absolute decline in the left ventricular ejection fraction (LVEF) by $> 10\%$ to $< 50\%$. The probability of stopping the trial for a true cardiac event rate of 4% and 8% was 38% and 83%, respectively. The secondary endpoints included the assessment of other toxicities and an exploratory analysis of serial cardiac biomarkers, including troponin I, B-type natriuretic peptide, and neuregulin-1β.

Patients

Eligible patients had histologically confirmed breast adenocarcinoma measuring ≤ 3.0 cm with HER2 immunohistochemistry (IHC) 3 + or fluorescent in situ hybridization (FISH) amplification (ratio ≥ 2.0), and no nodal involvement. Hematologic parameters included an absolute neutrophil count $\geq 1000/\mu L$, platelet count $\geq 100{,}000/\mu L$, normal total bilirubin, and transaminases < 2.5 of the upper limit of normal. A normal LVEF of $\geq 50\%$ on the echocardiogram (ECG) or multigated acquisition scan was required. Patients could not concomitantly use CYP3A4 inducers or inhibitors or drugs that can prolong the QTc interval. Patients with a known history of unstable angina, myocardial infarction, CHF, or serious medical illnesses were excluded. The institutional review board at Memorial Sloan Kettering Cancer Center approved the present study. Eligible patients were enrolled after providing written informed consent to participate.

Treatment

Treatment consisted of paclitaxel 175 mg/m^2 × 4 intravenously (IV) every 2 weeks, with IV trastuzumab (4 mg/kg load, 2 mg/kg weekly during chemotherapy, and then 6 mg/kg every third week afterward) and lapatinib (1000 mg orally daily). Filgrastim or pegfilgrastim was given during the paclitaxel phase. Both anti-HER2 therapies were given for 1 year (Figure 1).

Evaluations During Therapy

Evaluations, including complete blood count, liver function test, metabolic panel with potassium and magnesium, electrocardiograms, ECGs, and cardiac biomarkers were obtained at the time points outlined in Figure 1.

Toxicity Assessments and Dose Modifications

The toxicities were assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0. For paclitaxel, patients who experienced neutropenic fever and/or grade 3 or 4 nonhematologic toxicity had subsequent doses reduced by 25%. Only 1 dose reduction was allowed. Patients with grade 4 hypersensitivity reactions were removed from study. Dose modifications for trastuzumab were not permitted. With lapatinib, patients who experienced grade 3 or unacceptable grade < 2 toxicity related to lapatinib had the drug withheld for ≤ 21 days until improvement to grade < 1. One lapatinib dose reduction (1000 mg to 750 mg) was allowed. A second grade 3 event mandated withdrawal from the present study. The guidelines for the management of lapatinib-related diarrhea and rash are listed in Table 1.

Results

From May 2013 through November 2013, 20 of 55 planned patients were enrolled. All patients had early-stage breast cancer that was HER2 IHC 3+ or FISH-amplified, or both. The patient characteristics are listed in Table 2. Overall, 17 of the 20 patients (85%) had estrogen receptor-positive tumors. The tumor stage