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CLINICAL INVESTIGATION **Breast**

RADIOSENSITIZATION OF CHEMOTHERAPY-REFRACTORY, LOCALLY ADVANCED OR LOCALLY RECURRENT BREAST CANCER WITH TRASTUZUMAB: A PHASE II TRIAL

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Purpose: Trastuzumab (Herceptin), an anti-human epidermal growth factor receptor 2 (HER2) antibody, has been shown to be an effective radiosensitizer in preclinical studies. The present Phase II trial evaluated trastuzumab plus radiotherapy in patients with HER2-positive, chemotherapy-refractory, locally advanced or locoregionally recurrent breast cancer.

Methods and Materials: Eligible patients had measurable disease, normal cardiac function, and biopsy-confirmed residual HER2-positive disease. Patients received weekly trastuzumab (2 mg/kg intravenously), concurrent with radiotherapy (50 Gy) to the breast and regional lymph nodes for 5 weeks. If feasible, surgery followed radiotherapy. The primary endpoint was safety, and the secondary endpoint was efficacy (pathologic response and interval to symptomatic local progression).

Results: Of the 19 patients enrolled, 7 were ineligible and received radiotherapy alone and 12 received therapy per protocol. Of these 12 patients, 11 had a Stage T4 diagnosis. Grade 3 toxicities included skin ($n = 2$) and lymphopenia ($n = 1$). One patient experienced delayed wound healing after surgery. No patients developed symptomatic cardiac dysfunction. Of the 7 patients who had undergone mastectomy, 3 (43%) had a substantial pathologic response (complete response or microscopic residual disease), significantly more than a comparison cohort (2 of 38 or 5%, $p = .02$). The median interval to symptomatic local progression was not reached. The median overall survival was 39 months.

Conclusion: This is the first prospective trial providing evidence for a radiosensitizing effect of trastuzumab in breast cancer. The combination of trastuzumab and radiotherapy was well tolerated. © 2010 Elsevier Inc.

Neoadjuvant, radiotherapy, trastuzumab, breast cancer, radiosensitizer.

INTRODUCTION

The human epidermal growth factor receptor 2 (HER2) is overexpressed or gene amplified in 20–25% of breast cancers (1–3). Patients with HER2-positive disease have a less favorable prognosis than those with normal HER2 expression (1, 4). Trastuzumab (Herceptin, Genentech USA, South San Francisco, CA) is a monoclonal antibody that binds to HER2, resulting in inhibition of HER2-mediated downstream signaling and activation of antibody-dependent cellular cytotoxicity (5–7). In clinical trials, trastuzumab improved mortality outcomes in patients with metastatic and early breast cancer, either as monotherapy or combined with chemotherapy (8–12). Thus, trastuzumab has become a standard component of multimodality therapy for patients with HER2-positive breast cancer.

Radiotherapy (RT) is also a standard modality for the adjuvant treatment of breast cancer. RT is typically delivered after surgery, but it can also be used as primary therapy or, in some cases, preoperatively for locally advanced disease. However, the efficacy of RT is limited by the relative radioresistance of breast cancer cells. In preclinical studies, HER2 overexpression in breast cancer was associated with radioresistance relative to controls (low HER2 expression) (13). When HER2 is exogenously overexpressed in normal breast cancer cell lines, the HER2-overexpressing cells acquire radioresistance compared with their parental counterparts, a phenomenon that can be reversed with exposure to trastuzumab (13, 14). These results suggest that trastuzumab might be a radiosensitizer.

It remains unclear whether HER2 expression confers clinical radioresistance. Although Haffty *et al.* (15) found that

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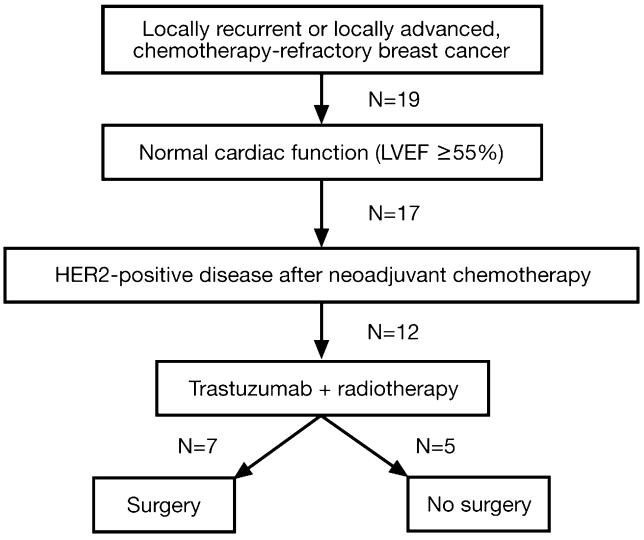

Fig. 1. Patient cohorts. Of 19 enrolled patients, 7 proceeded to final pathologic evaluation after protocol treatment. HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction.

breast tumors recurring after RT were more likely to overexpress HER2 than were case controls, others have found that the rate of locoregional recurrence after mastectomy was not greater in HER2-positive breast cancer (16). Prospective studies should help to clarify the role of HER2 in clinical radiation response.

Both trastuzumab and RT have been associated with cardiac dysfunction. In a Phase III metastatic breast cancer trial, the incidence of cardiac dysfunction (both asymptomatic and symptomatic) was 27% for patients receiving trastuzumab plus an anthracycline and cyclophosphamide (8). The incidence of cardiac events in the four large adjuvant trials, in which trastuzumab was not given concomitantly with doxorubicin and cyclophosphamide ranged from 0.4% to 3.8% compared with 0.1–0.9% in the nontrastuzumab arms and RT was given, as appropriate, after chemotherapy (12, 17–20). In most cases, the cardiac dysfunction associated with trastuzumab has been medically managed with standard medications and has been reversible in some cases, returning to baseline or close to baseline (21).

Cardiotoxicity has also been reported as a long-term complication for patients who undergo adjuvant RT (22, 23). As a result, concurrent delivery of trastuzumab and RT to the internal mammary nodal (IMN) chain was specifically prohibited in the adjuvant setting (11). However, modern techniques reduce radiation exposure to the heart and help minimize cardiotoxicity. Given the clinical benefit achieved with trastuzumab, it is important to assess both the improvement in locoregional control conferred by the addition of trastuzumab to RT and the risk of cardiac dysfunction.

To prospectively evaluate trastuzumab as a radiosensitizer, we initiated a Phase II clinical trial of concurrent trastuzumab plus preoperative or primary RT for patients with locally advanced HER2-positive breast cancer who had had less than a partial response to neoadjuvant chemotherapy or had locoregionally recurrent disease. The primary objective was safety, including cardiac function, acute skin toxicity, and wound healing complications. The secondary objective was efficacy. The primary efficacy endpoint was the pathologic response in patients who subsequently underwent resection, and the secondary efficacy endpoint was the interval to symptomatic local progression (SLP).

METHODS AND MATERIALS

The institutional investigative research board approved the study protocol, and all patients provided written informed consent. An overview of the trial design is presented in Fig. 1.

Eligibility

All patients were candidates for preoperative or primary RT, primarily because of a less than partial response to neoadjuvant chemotherapy. Patients had biopsy-proven HER2-positive (immunohistochemistry 3+ or amplified by fluorescence *in situ* hybridization), invasive breast cancer with measurable or evaluable locoregional disease after neoadjuvant chemotherapy or (from 2003 onward) locoregionally recurrent disease. The patients were confirmed to have Stage III or IV disease by clinical and radiographic staging and evaluated using the TNM scoring system (American Joint Committee on Cancer, 5th or 6th edition [24, 25]). The patients were eligible with any T stage plus N2 or N3 disease, T4 disease with any N stage, or distant metastasis with locally advanced disease in the breast/lymph nodes. Patients were excluded if they had received previous RT to the breast or regional lymph nodes.

Patients were initially excluded if their cardiac function after chemotherapy was less than the institutional limits of normal. However, institutional data had indicated that a mild, asymptomatic, cardiac function decline, as determined by multiple gated acquisition (MUGA) scans, frequently occurs in the acute period after neoadjuvant anthracycline chemotherapy (26). A recovery to full cardiac function was usually achieved. Therefore, the protocol was amended to include patients with modest cardiac dysfunction after previous therapy (decline in left ventricular ejection fraction [LVEF] <10% and asymptomatic). Patients who had a more significant or symptomatic cardiac decline after chemotherapy remained ineligible for concurrent trastuzumab.

Initially, patients were required to undergo repeat biopsy after neoadjuvant systemic therapy (which typically included trastuzumab) to confirm residual HER2-positive disease that could potentially be sensitized by trastuzumab. However, as it became clear that conversion from HER2-positive to HER2-negative disease occurs rarely, the requirement for biopsy was discontinued (6, 27).

Although the type of neoadjuvant therapy was not defined by protocol, most patients received four cycles of doxorubicin and cyclophosphamide followed by four cycles of paclitaxel every 3 weeks, given concurrently with weekly trastuzumab. After chemotherapy, the patients were assessed by physical examination, mammography, and ultrasonography, with or without additional radiographic studies. Patients without a treatment response were those with <50% (product of the craniocaudal and transverse diameters) decrease in measurable tumor (minimal response), no change in tumor size (stable disease), or increase in measurable tumor size by >50% (progressive disease). Preoperative RT was recommended due to either frankly inoperable disease or significant residual disease burden.