Annals of Surgical Oncology, **7**(1):145–149
Published by Lippincott Williams & Wilkins

Preoperative Paclitaxel and Radiotherapy for Locally Advanced Breast Cancer: Surgical Aspects

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Introduction: Approximately 15% of breast cancer patients present with large tumors that involve the skin, the chest wall, or the regional lymph nodes. Multimodality therapy is required, to provide the best chance for long-term survival. We have developed a regimen of paclitaxel, with concomitant radiation, as a primary therapy in patients with locally advanced breast cancer.

Methods: Eligible patients had locally advanced breast cancer (stage IIB or III). After obtaining informed consent, patients received paclitaxel (30 mg/m^2 during 1 hour) twice per week for 8 weeks and radiotherapy to 45 Gy (25 fractions, at 180 cGy/fraction, to the breast and regional nodes). Patients then underwent modified radical mastectomy followed by postoperative polychemotherapy.

Results: Twenty-nine patients were enrolled. Of these, 28 were assessable for clinical response and toxicity, and 27 were assessable for pathological response. Objective clinical response was achieved in 89%. At the time of surgery, 33% had no or minimal microscopic residual disease. Chemoradiation-related acute toxicity was limited; however, surgical complications occurred in 41% of patients.

Conclusions: Preoperative paclitaxel with radiotherapy is well tolerated and provides significant pathological response, in up to 33% of patients with locally advanced breast cancer, but with a significant postoperative morbidity rate.

Key Words: Locally advanced breast cancer—Paclitaxel—Radiotherapy—Mastectomy—Surgical morbidity.

Approximately 15% to 20% of women with breast cancer present with large tumors, often accompanied with advanced changes in the breast (ulceration, and skin or chest wall fixation) or lymph node involvement. These patients are at a high risk of both local and systemic failure despite aggressive treatment. Previously, locally advanced breast cancers were treated with radiotherapy alone, with 5-year survival rates ranging from 10% to 40%.[1,2] In the past 20 years, systemic polychemotherapy has been used in an attempt to improve the outcome in these patients. Recent studies that used induction chemotherapy have presented 5-year survival rates ranging from 40% to 50%, and the combination of chemotherapy with radiotherapy sequentially has led to a 5-year relapse-free survival rate of 45%.[3]

Paclitaxel produces objective responses in 50% to 60% of patients with metastatic breast cancer, when used as an initial therapy, and produces objective responses in 20% to 25% of patients with advanced disease who have failed other regimens.[4–9] Further, prospective randomized trials have shown that paclitaxel is as effective as a single agent as polychemotherapy regimens in both advanced breast cancer and in operable breast cancer.[10,11] The rationale for combining paclitaxel with radiotherapy has been described elsewhere.[12,13] We have studied the use of a regimen of preoperative paclitaxel with concurrent radiotherapy in patients with locally advanced breast cancer. The objectives of the study were (1) to evaluate the safety and feasibility of preoperative paclitaxel with concurrent radiotherapy in patients with locally ad-

Received June 11, 1999; accepted September 22, 1999.

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Presented at the 52nd Annual Meeting of Society of Surgical Oncology, Orlando, Florida, March 4–7, 1999.

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vanced breast cancer, generating in vivo human data on its pathological effects, and (2) to study the original biological characteristics of the tumor and to explore associations between the biological findings and the pathological response induced by paclitaxel and radiation. The biological studies will be completed when all 40 patients have been accrued. We report, here, the clinical results in the first 28 patients because of an increased rate of occurrence of surgical complications observed with this neoadjuvant regimen.

PATIENTS AND METHODS

The protocol was approved by the Institutional Review Board of our institution. Informed consent was obtained from all patients before enrollment. Patients were eligible if they were more than 18 years of age and had biopsy (cytologically or histologically) proven locally advanced breast cancer, stage IIB (T3N0), stage IIIA (T0N2, T1N2, T2N2, or T3N1–2), or stage IIIB (T4N0–2). Other eligibility requirements included an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1, measurable disease, no previous treatment, and medical and psychological ability to comply with the study requirements. Exclusion criteria included pregnancy, T1 or T2 disease, previous radiation or chemotherapy, presence of distant metastases documented either clinically or radiographically, or inflammatory breast cancer.

Pretreatment evaluation included the patient's history and a complete physical examination with measurement of all assessable lesions. Laboratory tests included a complete blood count with differential, electrolytes, blood urea nitrogen, creatinine, liver function tests, urinalysis, and a pregnancy test, if applicable. Radiological studies included bilateral mammography, posterior–anterior and lateral chest radiographs, and computed tomographic scans of the chest, abdomen, and pelvis in all patients. A bone scan was performed in symptomatic patients or if the concentration of alkaline phosphatase was elevated. All patients underwent core biopsy of the primary tumor and any palpable lymph nodes within a week of beginning therapy for baseline tumor studies and molecular studies. In all patients, the two largest perpendicular diameters of the palpable breast tumor were marked with skin tattoo dots before initiating therapy, to facilitate follow-up measurements and resection, in the event of complete response.

Initially, the study was designed with patients receiving paclitaxel, 60 mg/m^2 weekly, and radiotherapy to the breast and regional lymph nodes, to a total dose of 50 Gy (2 Gy/fraction during 5 weeks). Because both of the first two patients treated experienced severe toxicity,[12] the protocol was modified as follows: Within 7 days of the biopsies, the patient began treatment with paclitaxel 30 mg/m^2, as a 1-hour intravenous infusion twice per week for a total of 8 weeks. Within a week of beginning treatment with paclitaxel, daily radiotherapy to the breast and regional lymph nodes was added, to a total dose of 45 Gy (1.8 Gy/fraction during 5 weeks). After the completion of radiotherapy, the patient completed the final 2 weeks of the paclitaxel regimen without radiation, which allowed the radiation changes to subside. Tumor response was assessed weekly by physical examination. The study design provided that if disease progressed while the patient received the primary paclitaxel/radiation regimen, the patient would go immediately to surgery if deemed operable. If deemed inoperable, the patient would be switched to an Adriamycin (doxorubicin HCl)-based polychemotherapy regimen. At the completion of the paclitaxel/radiation regimen, the patient was assessed for clinical response by physical examination. Patients who were believed to be operable underwent modified radical mastectomy (MRM) when the skin had recovered from the acute side effects of the radiation (at least 2 weeks from the last day of radiation). Inoperable patients were referred for further Adriamycin-based polychemotherapy. Postoperatively, patients received Adriamycin-based polychemotherapy for four cycles. In addition, for all estrogen receptor-positive patients, a 5-year course of tamoxifen was prescribed.

Outcome measures included resectability, clinical response, pathological response, toxicity, and operative morbidity rate. Clinical response was defined as complete (CR) if no residual tumor was identified on physical examination, partial (PR) if there was a more than 50% reduction in the size of the primary tumor, and no response (NR) if there was less than 50% reduction in the size of the primary tumor. Patients who progressed while receiving treatment were classified separately. Pathological response was defined as complete (pCR) if no residual tumor cells were identified in the mastectomy specimen, and partial (pPR) if only minimal ($<$10 foci) microscopic disease remained. Patients with persistent disease on pathological examination were considered pathological nonresponders (pNR). Correlation between clinical response and pathological response was determined by using Fisher's exact test. Toxicity was classified by National Cancer Institute criteria. Anything other than perfect primary healing of the operative wound was considered a postoperative complication.

RESULTS

Twenty-nine patients were enrolled. Of these, 28 have completed the regimen and were assessable for toxicity and clinical response. Twenty-seven patients were assessable for pathological response. One patient refused surgery after achieving a clinical PR at the completion of the preoperative regimen, and one patient has yet to complete the regimen. The characteristics of the 27 patients undergoing surgery and their tumors are summarized in Table 1. The mean age of the patients was 51 years (range, 30–74 years). Twenty-four patients had ECOG scores of 0, and three patients had scores of 1. Seven patients had stage IIB disease (T3N0), 10 had stage IIIA disease, and 10 had stage IIIB disease.

Seventeen patients (59%) had clinically involved axillary nodes at the time of presentation. Of these, nine were clinically node negative at the completion of the preoperative regimen. Fifteen patients had pathological node involvement, all but one of whom had been clinically node positive at the beginning of the regimen. Pathological nodal status correlated with both pretreatment clinical nodal status ($P = .0008$; Fisher's exact test) and posttreatment clinical nodal status ($P = .0433$; Fisher's exact test).

Two of the 28 patients achieved a clinical CR (7%), 23 of the 28 patients had a clinical PR (82%), and 3 patients had stable disease (NR). No patient progressed on the preoperative regimen. All patients were judged operable at the completion of the regimen. The first two patients treated, who received paclitaxel 60 mg/m^2 in a once-a-week dosing and radiation at 200 cGy/fraction, had such a vigorous skin and tumor response that the degree of desquamation, necrosis, and subsequent scarring required flap reconstruction after mastectomy for cosmesis. This experience led to subsequent patients being treated with twice-a-week dosing, and no similar problems have since been encountered. Two patients who had clinical a PR deviated from the protocol by requesting breast preservation rather than undergoing mastectomy. Based on the tattoo markings of the original tumor volume, they both underwent partial mastectomy with axillary lymphadenectomy. The remaining 23 patients underwent MRM with primary wound closure. In all cases, surgical margins were free of tumor at pathology.

Of the 27 patients who underwent surgery, 7 (26%) patients had a complete pathological response (pCR), with no viable invasive tumor remaining in the resected specimen. Two (29%) of these patients did have residual ductal carcinoma in situ in the specimen. Two (7%) patients had a partial pathological response (pPR), with only minimal microscopic disease remaining. The remaining patients had significant residual disease on pathological examination (pNR). Thus, of the 24 patients who had a clinical response, only 9 (35%; 95% confidence interval = 20%–59%) had a pathological response, suggesting that clinical response does not necessarily predict pathological response.

The chemoradiation-related morbidity rate was minimal. Treatment feasibility is reported elsewhere.[14] The surgical morbidity rate was significant and is summarized in Table 2. All of the patients undergoing flap reconstruction or breast conserving surgery, and one-third of the patients undergoing MRM, experienced some

TABLE 1. *Patient and initial tumor characteristics of 27 assessable locally advanced breast cancer patients treated with preoperative paclitaxel with concomitant radiotherapy*

Characteristic	No. (%)
Age[a], y	
≤50	15 (56)
>50	12 (44)
ECOG score	
0	24 (89)
1	3 (11)
Initial tumor size	
T3	17 (63)
T4	10 (37)
Initial clinical lymph node status	
N0	11 (41)
N1	14 (52)
N2	2 (7)
Stage at diagnosis	
IIB	7 (26)
IIIA	10 (37)
IIIB	10 (37)

ECOG, Eastern Cooperative Oncology Group.
[a] Median age was 47 years.

TABLE 2. *Surgical complications after preoperative paclitaxel with concomitant radiotherapy*

Procedure/complication	No. of patients
Modified radical mastectomy with TRAM reconstruction (treated with paclitaxel 60 mg/m^2 and radiation at 200 cGy/fraction)	2
Flap failure requiring revision	1
Flap separation with infection during postoperative chemotherapy	1
Breast conservation therapy	2
Chronic radiation mastitis (recall) during postoperative chemotherapy	2
Modified radical mastectomy	23
Patchy flap necrosis, delayed healing	4
Recurrent hematoma	1
Recurrent seroma, infected seroma	1
Wound cellulitis	1
Decreased range of motion, upper extremity	1

TRAM, transverse rectus abdominis myocutaneous flap.

type of complication. The two patients treated with paclitaxel 60 mg/m^2 and radiation at 200 cGy/fraction both underwent MRM with transverse rectus abdominis myocutaneous flap reconstruction. One patient developed failure of the superior portion of the flap on the third postoperative day, requiring flap revision. She subsequently did well. The other patient developed wound separation and an infection around her flap after her second cycle of postoperative chemotherapy and had significantly delayed wound healing, requiring 2 months of local wound care. Two patients were treated with partial mastectomy after treatment with paclitaxel and radiation. They both developed a chronic noninfectious mastitis caused by radiation recall, the paclitaxel, or to the combination, that persisted throughout their postoperative chemotherapy course.

Of the 23 patients treated with MRM, 4 developed patchy flap necrosis that led to significantly delayed wound healing (3 weeks to 3 months), 1 of whom, who was an elderly diabetic patient, also had a recurrent hematoma under her skin flap. One patient developed a recurrent axillary seroma that ultimately became infected. One patient developed a wound cellulitis requiring admission for intravenous antibiotics. One patient has a persistent decreased range of motion of the upper extremity despite vigorous rehabilitation. No patient has developed early lymphedema, despite undergoing axillary irradiation followed by axillary lymphadenectomy (18 patients underwent a complete [levels I, II, and III] dissection and 9 underwent a level I and II dissection; mean number of nodes removed = 15; range, 7–33).

DISCUSSION

Multimodality therapy has become the standard of care in the treatment of locally advanced breast cancer. The optimal regimen and sequencing has yet to be determined. The combination of preoperative paclitaxel with concomitant radiotherapy was effective in reducing tumor size in patients presenting with T3 or T4 disease. Eighty-nine percent of patients in this study had an objective clinical response, and all patients could be resected with negative surgical margins. Toxicity of the regimen was limited. Thirty-three percent of patients achieved a pathological response, with no or minimal microscopic residual disease at the time of the pathological examination. These results compare favorably with results from other neoadjuvant regimens in similar patient populations.[15–20]

Surgical morbidity rate was an issue throughout the study. Both patients treated with paclitaxel 60 mg/m^2 and radiation at 200 cGy/fraction, who underwent transverse rectus abdominis myocutaneous flap reconstruction, had a significant complication. One patient had failure of her flap, which required revision on postoperative day 3. The other patient experienced partial separation of her flap, during her postoperative chemotherapy regimen, with subsequent wound infection and delayed healing. Recall of the radiation effects by both paclitaxel and Adriamycin likely contributed to this, and they must be considered a source of potential problems in regimens involving preoperative radiation.[21–25] Modifying the protocol to twice-a-week dosing eliminated the need for flap reconstruction with the associated complications.

Another example of the recall of paclitaxel/radiation effects on normal tissue was observed in the two patients who deviated from the protocol and underwent breast-conserving surgery. Both patients developed a chronic radiation mastitis (noninfectious) that persisted throughout the course of their postoperative chemotherapy regimen. Although this was not life threatening, or detrimental to the patient's health, it was bothersome, and, at times, quite painful, requiring acetaminophen with codeine for pain control. These patients elected to deviate from the protocol because they had both achieved such a significant clinical response that they wanted to attempt to save their breasts. It has become increasingly clear that there is, indeed, a synergism between paclitaxel and radiation.[13] However, the response rates we observed in this study were not superior to those reported while using either polychemotherapy regimens or other chemoradiation regimens.[20] There have been no trials that compared paclitaxel alone to paclitaxel with concomitant radiation in the setting of locally advanced breast cancer. Although conventional wisdom suggests that achieving a pathological complete response leads to improved survival, there is no evidence that driving pathological response with local measures, such as the addition of radiotherapy, adds to long-term survival. It would be of interest to test this hypothesis in a prospective randomized fashion.

Finally, 7 of the 23 patients who underwent mastectomy had complications. Most of the complications were minor wound complications that were easily managed, and they were likely related to the synergistic effects of paclitaxel and radiation.

We previously published a series in which we evaluated the surgical results of a regimen of preoperative continuous infusion of 5-fluorouracil with concomitant radiotherapy in patients with inoperable locally advanced breast cancer.[20] This regimen had minimal treatment-related toxicity and was quite effective, producing objective tumor responses in 73% of patients and rendering 100% of patients resectable with primary wound closure and negative surgical margins. Further, there was no significant increase in the operative

morbidity rate with the 5-fluorouracil regimen. The current regimen is in stark contrast. Postoperative complications were observed in 41% of patients who, in general, had significantly less extensive disease at the time of enrollment. Although most of the complications were wound related and self limited, and none was life threatening, they must be considered in the risk/benefit analysis for this regimen.

Our group has focused on studying potential molecular markers that predict response to specific chemoradiation regimens. All patients in this study had pretreatment biopsies that may enable us to identify who could most benefit from this treatment. Although the high rate of occurrence of surgical morbidity without significantly improved response rates precludes recommending this regimen for all patients with locally advanced breast cancer, it is possible that biological studies may identify a subgroup of patients for whom the benefits of the regimen outweigh the increased risks.

Acknowledgment: Supported, in part, by grants from the California Breast Cancer Research Program (3DB-0045 and 4EB-6000).

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