Neoadjuvant Concurrent Paclitaxel and Radiation in Stage II/III Breast Cancer

A. Bapsi Chakravarthy,1 Mark C. Kelley,2 Bernadette McLaren,3 Cristina I. Truica,6 Dean Billheimer,4 Ingrid A. Mayer,6 Ana M. Grau,2 David H. Johnson,6 Jean F. Simpson,3 R. Daniel Beauchamp,2 Catherine Jones,6 and Jennifer A. Pietenpol5

Abstract

Purpose: The aim of this study was to determine the safety and pathologic response rates following neoadjuvant paclitaxel and radiation in patients with stage II/III breast cancer and to evaluate the use of sequential biopsies to allow an in vivo assessment of biological markers as potential predictive markers of response to this regimen.

Patients and Methods: Patients with high-risk, operable breast cancer were treated with three cycles of paclitaxel 175 mg/m² every 3 weeks, followed by twice-weekly paclitaxel 30 mg/m² and concurrent radiation. Core biopsies were obtained at baseline and 24 to 72 hours after the first cycle of paclitaxel. After completing neoadjuvant treatment, patients underwent definitive surgery. The primary end point was pathologic complete response, which is defined as the absence of any invasive cancer at surgery. Potential markers of therapeutic response were evaluated including markers of proliferation, apoptosis, p21, HER2, estrogen receptor, and progesterone receptor status.

Results: Of the 38 patients enrolled, 13 (34%) had a pathologic complete response. There was no significant difference in baseline Ki-67 between responders (35%) and nonresponders (28%; P = 0.45). There was also no significant change in Ki-67 following paclitaxel administration. Despite this lack of immunohistologic change in proliferative activity, baseline mitotic index was higher for patients with pathologic complete response over nonresponders (27 versus 10, P = 0.003). Moreover, the increase in mitotic index following paclitaxel administration was associated with pathologic complete response.

Conclusions: Neoadjuvant paclitaxel/radiation is effective and well tolerated. Tumor proliferation at baseline and response to chemotherapy as measured by mitotic activity may serve as an important indicator of pathologic response to neoadjuvant paclitaxel/radiation.

Although neoadjuvant chemotherapy is becoming the standard of care in locally advanced breast cancers (1, 2), there are few studies that have attempted to combine chemotherapy with radiation in the neoadjuvant setting (3–5). Frequently neoadjuvant chemotherapy involves anthracycline-based regimens and toxicity considerations preclude combining it with radiation. More recently, randomized trials have shown that clinical and pathologic response rates after neoadjuvant paclitaxel are equivalent to the previously used anthracycline-based regimens (6). Paclitaxel is increasingly being used as a single agent both in the adjuvant (7) and neoadjuvant settings (6).

Neoadjuvant therapy downsizes the tumor, allowing a less extensive surgical procedure, and allows early initiation of both systemic therapy and local therapy in patients at high risk for distant as well as local failure. More importantly, the use of sequential biopsies in the neoadjuvant setting allows an in vivo assessment of biological markers. Markers identified early in the course of a patient’s treatment could be used to modify subsequent therapy. Although hormone receptor status has proved to be an effective marker of therapeutic response to hormonal therapy (8) and HER2 status to herceptin therapy (9), biological markers of response to concurrent chemoradiation have yet to be well established.

In several studies, complete pathologic response to neoadjuvant chemotherapy has been associated with a significant survival advantage (1, 10). Changes in markers of proliferation and apoptosis can be measured as early as 24 hours after chemotherapy (11) and are often complete by 4 days (12). An early increase in apoptosis has been shown to correlate with clinical response (13).
With the advent of taxanes, concurrent chemoradiation can be reconsidered in the treatment of breast cancer. Paclitaxel is a potent radiosensitizer of which the precise mechanism of action remains unclear, especially in the in vivo clinical setting. Many studies have shown that paclitaxel binds to tubulin and induces an M-phase arrest. Given that cells in the M phase of the cell cycle are very sensitive to radiation (14, 15), paclitaxel-induced M-phase arrest is generally considered to be the mechanism of paclitaxel-induced radiosensitivity. In vitro treatment of epithelial tumor cells with paclitaxel induces an accumulation of cells in M phase by 12 to 24 hours (16, 17).

The primary goal of the current study was to determine the efficacy and safety of neoadjuvant paclitaxel followed by concurrent paclitaxel/radiation in the treatment of patients with stage II/III breast cancer. Secondary goals included evaluating biological markers including HER2, estrogen receptor, progesterone receptor, Ki-67, apoptosis [terminal deoxyribonucleotidyl transferase–mediated dUTP nick end labeling (TUNEL)], and mitotic index as potential predictive markers of response to this regimen. We hypothesized that patients with the greatest degree of M-phase arrest (as measured by mitotic index) would be more sensitive to the concurrent use of paclitaxel and radiation and have higher rates of pathologic responses.

**Patients and Methods**

**Patients and treatment.** Women ≥18 years of age with biopsy-proven infiltrating breast cancer, stages IIA to IIIA, and Eastern Cooperative Oncology Group performance status of 0 to 1 were enrolled on study. Patients signed a protocol-specific consent that was approved by the ethics committee of the participating centers of the Vanderbilt-Ingram Cancer Center Affiliate Network. Tumor measurements were obtained by physical exam, mammogram, and/or ultrasound before chemotherapy. Core biopsies were obtained before treatment as well as 24 to 72 hours after the first cycle of paclitaxel. Patients were required to have adequate metabolic functions within 4 weeks of study entry and fertile women had to use effective contraception. The treatment schema is outlined in Fig. 1.

**Neoadjuvant paclitaxel.** Phase I/II studies have established a variety of schedules for the administration of paclitaxel with neutropenia and neuropathy being the major dose-limiting toxicities. In a large randomized study that evaluated escalating doses of paclitaxel (175, 210, and 250 mg/m² in 3-hour infusions every 3 weeks), there was no difference in response rates or overall survival with increasing doses but there was an increase in toxicity (18). Therefore, we used paclitaxel 175 mg/m² as a 3-hour infusion every 3 weeks for three cycles as the initial neoadjuvant chemotherapy component of therapy. Before paclitaxel administration, patients were premedicated with oral dexamethasone.

**Neoadjuvant paclitaxel and radiation.** Three weeks following completion of neoadjuvant paclitaxel, patients received concurrent twice-weekly paclitaxel with radiation. Published reports had shown that a paclitaxel dose of 60 mg/m² weekly resulted in excessive toxicity but 30 mg/m² given twice-weekly with radiation to a dose of 4,680 cGy was well tolerated (4). In the current study, a total dose of 4,600 cGy in 28 fractions to the breast and 4,500 cGy in 25 fractions to the regional nodes was delivered. There was no attempt to treat the internal mammary nodes. During the concurrent paclitaxel/radiation component of the protocol, patients were premedicated with dexamethasone 10 mg 30 minutes before the first two doses of weekly paclitaxel (30 mg/m²).

**Surgery.** Patients went on to definitive surgery (consisting of lumpectomy or mastectomy) 3 to 4 weeks following completion of chemoradiation. After increased postoperative complications were noted in the first 12 patients, the protocol was modified to delay surgery 5 to 7 weeks after the last dose of radiation (19). The type of surgery was left to the discretion of the treating surgeon.

**Postoperative adjuvant therapy.** Four to six weeks following surgery, patients completed postoperative adjuvant chemotherapy consisting of doxorubicin 60 mg/m² i.v. over 20 minutes and cyclophosphamide 600 mg/m² i.v. given every 3 weeks for four cycles. Following completion of all chemotherapy, hormonal therapy (Tamoxifen or Arimidex) was given to women who were estrogen receptor and/or progesterone receptor positive.

**Response assessments.** Clinical response was classified as follows: (a) complete response, disappearance of all measurable disease; (b) partial response, a reduction of ≥50% in the sum of the products of the perpendicular diameters of the tumor; (c) stable disease, a 50% reduction or a ≥25% increase in the sum of the products of two perpendicular diameters of the tumor; and (d) progressive disease, an increase in the product of two perpendicular diameters of the tumor by >25% or the development of any new lesions.

Pathologic response was defined as follows: (a) complete responders, no residual viable tumor on histologic analysis—specimens containing only noninvasive disease were classified as complete responders; and (b) nonresponders, any viable tumor in breast or lymph nodes.

**Collection and timing of tissue samples.** In vitro studies in our laboratory showed an increase in mitotic arrest, hyperphosphorylation of Bcl-2, and subsequent cell death 24 hours after treatment with paclitaxel (17). Potential markers of therapeutic response were chosen based on these preclinical findings and tested prospectively on all patients who consented to having these biopsies done. Four to six core tissue samples were obtained using a tru-cut needle before and 24 to 72 hours after the first cycle of paclitaxel. One to two cores were placed in 10% formalin and embedded in paraffin for histologic evaluation. The remaining two to four core biopsies were immediately frozen and stored in −80°C freezer until processed.

**Laboratory methods.** Immunohistochemistry for Ki-67, p53, estrogen receptor, progesterone receptor, and HER2 was done using a standard avidin-biotin complex technique as described below. The apoptotic index was determined using TUNEL and in situ end-labeling techniques.

**Ki-67.** Slides were immunostained with commercially available antibodies. They were scored for percentage of positive cells by a single pathologist (B.M.) using light microscopy.

**Biopsy obtained pre-treatment for molecular markers at the time of diagnosis.**

↓

**Paclitaxel 175 mg/m² IV every 3 weeks x 3 cycles.**

↓

**Biopsy obtained 24-72 h after first cycle of paclitaxel for molecular markers.**

↓

**Radiation 4680 cGy/26 fractions with concurrent paclitaxel 30 mg/m², twice per week.**

↓

**Surgery (MRM or lumpectomy, at discretion of treating surgeon).**

↓

**Doxorubicin 60 mg/m², cyclophosphamide 600 mg/m² IV every 3 weeks x 4 cycles**

↓

**Hormonal therapy (at discretion of treating oncologist).**

Fig. 1. Treatment schema. MRM, modified radical mastectomy.
Mitotic index. Mitotic index was defined as the number of mitoses in 10 successive high-power fields using a microscope with a 40×/0.70 objective and a 10× ocular. Each field corresponded to a surface of 3.3 mm². Mitotic count was done by a single pathologist (B.M.) on H&E-stained paraffin sections prepared from core needle biopsies.

Statistical analysis. This study was designed to evaluate the toxicities of neoadjuvant paclitaxel and radiation before surgery. It allowed us to estimate rates of clinical and pathologic responders in this setting. The primary end point was complete pathologic response as defined by the absence of invasive cancer in the breast or lymph nodes. The relationship between pathologic complete response and potential markers of therapeutic response was examined. These markers included Ki-67, apoptosis (TUNEL), mitotic activity as measured by number of cells in mitosis per 10 high-power fields, p21, HER2, estrogen receptor, and progesterone receptor status. Pearson’s χ² test was used to determine the association of categorical variables to pathologic complete response. Logistic regression was used to evaluate the effect of continuous variables on pathologic complete response. The change between pretreatment and posttreatment markers was assessed using the Wilcoxon test for a shift in the mean. As this study is largely exploratory, we assessed all associations at the 0.05 significance level (two sided).

Results

Patient characteristics. Thirty-eight patients were enrolled onto this study between April 2000 and March 2004. Baseline patient characteristics are described in Table 1. The median follow-up time after surgery was 23 months (range, 1-46 months).

The flow of patients through the study is outlined in Fig. 2. Of the 38 patients who initially enrolled, two progressed during chemotherapy and went directly to surgery. One received only one cycle of paclitaxel due to noncompliance and one patient received only two cycles due to toxicity. During the interval of time between completing chemoradiation and surgery, two patients withdrew and two progressed. All 38 patients were evaluable for toxicity from the neoadjuvant paclitaxel.

Twenty-eight of the 30 patients who began concurrent chemoradiation component of therapy completed it. All 30 patients were evaluable for toxicity of concurrent chemoradiation. One patient developed metastatic disease shortly after completing the chemoradiation phase of therapy and was therefore not taken to surgery.

Of the initial 38 patients who enrolled, four progressed locally and four did not complete all phases of therapy. Except for one patient who developed metastatic disease before surgery, 37 patients went on to definitive surgery. Fifty-seven percent of patients (21 of 37) underwent modified radical mastectomy and 43% (16 of 37) underwent lumpectomy. All 37 patients were evaluable for postoperative morbidity.

Toxicities by phase of therapy. Patients tolerated the initial three cycles of neoadjuvant paclitaxel 175 mg/m² well with 89% (34 of 38) receiving all three cycles of planned chemotherapy at full dose and on schedule. Grade 3 toxicities included thromboembolism (n = 1), hyperglycemia (n = 4), hypoglycemia (n = 1), and joint pain/arthralgia/myalgia (n = 4). There were no grade 4 toxicities.

Patients tolerated the concurrent chemoradiation phase of the study well with 87% (26 of 30) of patients completing full doses of the planned twice-weekly paclitaxel. There were no dose reductions or delays due to toxicity. Grade 3 toxicity included moist skin desquamation (n = 1), fatigue (n = 1), and liver function abnormalities (n = 1). One patient suffered a grade 4 skin reaction. All patients completed the planned 4,680-cGy radiation.

Although only 28 of the 38 patients completed all phases of neoadjuvant therapy, 37 of 38 went on to definitive surgery.
Postsurgical complications are summarized in Table 2. Of the three patients who underwent transverse rectus abdominis myocutaneous flap reconstruction, two required revisions.

Of the 38 patients, 28 began postoperative chemotherapy consisting of four cycles of doxorubicin/cyclophosphamide. One patient elected not to complete the planned chemotherapy and two patients were taken off due to toxicity. The remaining 21 of 25 patients received full doses of chemotherapy, 1 required a dose reduction due to toxicity, and 7 patients required doses to be delayed. Grade 3 toxicities included anemia (n = 3), neutropenia (n = 7), and wound infections (n = 4). Grade 4 toxicities included neutropenia (n = 3).

Response. Thirty-four percent (13 of 38) had a pathologic complete response. Of the initial 38 patients, 4 patients withdrew from the study before surgery. Of the remaining 34 patients who went on to surgery, 38% (13 of 34) had a pathologic complete response. There was a greater correlation between clinical and pathologic findings for patients who had a complete pathologic response over patients who did not respond to therapy. Eighty-six percent of patients (6 of 7) who showed a complete clinical response also had a complete pathologic response. With a median follow-up of 23 months (range, 1-46 months), the median survival from initial diagnosis was 22.5 months (range, 5.7-51.3 months).

Biological markers. Although every attempt was made to get paired samples on all patients, this was not always possible. At times, insufficient tissue required the prioritizing of marker studies that would be done.

Baseline Ki-67 and mitotic index. Although the large majority of studies using Ki-67 have correlated its expression with clinical outcome, few have used it as a predictive marker of response to specific therapy. We hypothesized that patients with higher proliferative rates at the time of initial presentation would be more responsive to paclitaxel treatment. Although pretreatment Ki-67 was higher for responders (35%) versus non-responders (28%), this was not statistically significant (Fig. 3A).

Mitotic index was also evaluated at baseline and correlated to pathologic response. We found a statistically significant difference in baseline pretreatment mitotic index in patients who had a complete pathologic response (mean mitotic index = 27) over patients who did not (mean mitotic index = 10; P = 0.003; Fig. 3B).

Serial changes in Ki-67 and mitotic index. Contrary to our initial hypothesis that patients who showed the greatest decrease in proliferation rates following paclitaxel would show the highest response rate, there was no significant change in Ki-67 following paclitaxel (Fig. 4A and B).

M phase. On the other hand, in 92% (22 of 24) of patients, there was an increase in mitotic index 24 to 72 hours following the administration of paclitaxel. Following the administration

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**Table 2. Postsurgical complications**

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Abbreviations: MRM, modified radical mastectomy; TRAM, transverse rectus abdominis myocutaneous.

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**Fig. 3.** Baseline Ki-67 and mitotic index as predictors of pathologic response. Y axis, percentage of cells staining positive for Ki-67 (A) and mitotic index (B). Each point represents one patient. Horizontal lines, mean Ki-67 and mitotic index. Vertical lines, mean separation lines. If the vertical lines do not overlap, the means differ at the 0.05 significance level using a t test. Mitotic index, number of mitoses per 10 high-power fields using a 40×/0.70 objective and a 10× ocular. CR, complete responders; no invasive cancer seen on pathologic evaluation. NR, nonresponders; residual tumor at surgery.
of paclitaxel, tumors that showed the greatest degree of change in mitotic index from pretreatment levels also resulted in a pathologic complete response (Fig. 4C and D).

In addition to Ki-67 and mitotic index, we tested several biomarkers (progesterone receptor, HER2, p53, p21, and TUNEL) for their potential to predict pathologic complete response rates. None of these showed a statistically significant ability to act as predictors of response. There was a trend towards higher pathologic response rates in higher-grade tumors ($P = 0.12$) and estrogen receptor–negative tumors ($P = 0.05$).

**Discussion**

The primary goal of this study was to determine the overall pathologic complete response rate of neoadjuvant paclitaxel followed by concurrent paclitaxel/radiation in patients with stage II/III breast cancer. Secondary goals included determining the safety of this sequencing and evaluating biological markers of response including HER2, estrogen receptor, progesterone receptor, Ki-67, apoptosis (TUNEL), and mitotic index as potential markers of response to this regimen.

Our pathologic complete response rate of 34% compares favorably with other studies that have used concurrent neoadjuvant paclitaxel/radiation in locally advanced breast cancer where pathologic complete response rates were ~35% (3, 20). This is in contrast to studies using neoadjuvant chemotherapy alone where pathologic complete response rates are generally limited to 10% to 15% (1, 21). In trials that used weekly paclitaxel in the neoadjuvant setting, the pathologic complete response rates have been higher than in every-3-week regimens (28% versus 15%; ref. 22). Although pathologic complete response rates have correlated with disease-free and overall survival in patients who have received neoadjuvant chemotherapy, whether pathologic complete response rates after concurrent chemoradiation carry the same predictive potential is unknown. The ability of the intact breast mass to act as an *in vivo* assay of micrometastatic disease may not apply when the mass is also being treated by a local modality that would not be expected to affect these micrometases. If, however, control of the primary tumor can prevent future micrometastatic spread, achieving greater pathologic response in the primary tumor may ultimately lead to better overall survival.

We show that neoadjuvant paclitaxel followed by concurrent paclitaxel/radiation is well tolerated. One of the major concerns of combining paclitaxel and radiation has been pneumonitis. Symptomatic pneumonitis has varied from 0% to 20% (23–26). The reasons for these differing results is unclear but may be related to differences in the dosing and sequencing of paclitaxel with radiation. In studies that showed unacceptable toxicity, the majority of the patients had received bolus paclitaxel at 175 mg/m$^2$ on a 3-week regimen. The two patients who developed pneumonitis on the weekly regimen had received higher weekly doses of 80 to 90 mg/m$^2$ of paclitaxel than was used in our study. No instances of radiation pneumonitis were seen either in our study or in another study of neoadjuvant concurrent paclitaxel/radiation using twice-weekly 30 mg/m$^2$ of paclitaxel (5).

A second major concern in the use of preoperative chemoradiation is the development of postoperative complications. Despite delaying surgery for at least 5 weeks following...
chemoradiation, almost half the patients had some postoperative morbidity and 4 of 37 (10%) had complications requiring further interventions (i.e., antibiotics and seroma drainage). Others have also found higher rates of surgical complications following neoadjuvant chemoradiation despite delaying surgery until skin recovery was achieved (27). Our study, as well as that of Skinner et al. (27), found that complications were greater in patients who underwent mastectomies over patients who were able to undergo breast conservation.

In addition to the primary end points of pathologic response rates and safety of this novel sequencing, we examined prospectively potential markers of therapeutic response including markers of proliferation, apoptosis, p21, HER2, estrogen receptor, and progesterone receptor status. Baseline proliferative activity, as measured by Ki-67, did not correlate with pathologic response. Few studies have correlated the predictive value of Ki-67 with pathologic response and none have examined its role following neoadjuvant chemoradiation. Similarly, we did not observe a significant change in proliferative activity as measured by Ki-67 in sequential core biopsies following paclitaxel. Our data suggest that chemosensitivity to paclitaxel is not a simple function of baseline proliferative activity.

Additional biomarkers, including progesterone receptor, HER2, p53, p21, and TUNEL, did not correlate with pathologic response. Estrogen receptor–negative tumors did show a trend towards a higher rate of pathologic response. On the other hand, a higher baseline mitotic index before neoadjuvant chemotherapy and an increase in mitotic index on sequential core biopsies following paclitaxel administration correlated with pathologic complete response.

Although mitotic index has been hypothesized by several investigators to be a prognostic factor in breast cancer (28), to date, there have not been any studies that evaluate its role as a predictive marker of response to chemoradiation. The results of this clinical study support preclinical studies that have shown that paclitaxel arrests cells in M phase of the cell cycle, resulting in an increase in mitotic index 24 to 72 hours after paclitaxel (29, 30).

It is interesting that the two markers of proliferation, Ki-67 and mitotic index, behaved differently to a single dose of paclitaxel. Despite little change in proliferation as measured by Ki-67, there was an increase in mitotic index. This discrepancy may be due to the fact that Ki-67 is an indirect measure of proliferation, which depends on an antigen-antibody reaction, whereas mitotic index is a direct measure of the number of cells undergoing mitosis following paclitaxel. Others have also found that the use of identifiable mitotic figures using a microscope was predictive of pathologic response following neoadjuvant chemotherapy (12). In light of the fact that other markers of proliferation, such as Ki-67 and percentage of cells in S-phase, have been validated and used in the clinical setting, our results provide preliminary evidence that mitotic index could also be considered in such a setting.

Our study is limited by the small sample size. Obviously, the predictive power of mitotic index needs to be validated in a larger study. A prospective trial has shown that a high mitotic index is associated with efficacy of adjuvant anthracycline-based chemotherapy (31). There are no large prospective studies that have evaluated it as a predictive marker of response to paclitaxel/radiation. In the future, information from such biopsies could allow subsequent therapy to be modified based on an individual’s response to a particular drug or drug/radiation combination. Finally, these core biopsy specimens are a valuable resource for additional studies to determine whether RNA microarray expression profiling or DNA array gene amplification/gene loss patterns can be used to predict an individual patient’s response to concurrent paclitaxel/radiation.

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