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CLINICAL INVESTIGATION **Breast**

CONCURRENT RADIATION THERAPY AND PACLITAXEL OR DOCETAXEL CHEMOTHERAPY IN HIGH-RISK BREAST CANCER

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Purpose: Evidence supports the inclusion of the taxanes in the treatment of breast cancer. A recent randomized trial has shown a survival advantage to the addition of paclitaxel in the adjuvant treatment of node-positive patients. Several studies have suggested diminished local control if adjuvant radiation is delayed, while *in vitro* and *in vivo* studies have demonstrated a benefit of concurrent administration of taxanes with radiation. For these reasons, we began in 1995 to administer radiation therapy concurrently with the taxanes in advanced breast cancer. This retrospective review examines the feasibility of such treatment.

Methods and Materials: Forty-four patients were treated with concurrent radiation and either paclitaxel (29 patients) or docetaxel (15 patients). One patient received both paclitaxel and docetaxel. Eighteen patients were treated for recurrent disease, 9 had received prior radiation. Toxicity was assessed by the RTOG scale for acute and late effects.

Results: Concurrent radiation and taxane chemotherapy was well tolerated. Nine patients (20%) experienced Grade 3 acute skin toxicity. This was more likely with docetaxel than paclitaxel ($p = 0.04$). Among patients undergoing breast conservation, there were no Grade 3 toxicities. With a median follow-up of 11 months, 1 patient has developed breast fibrosis.

Conclusion: Concurrent administration of both paclitaxel and docetaxel with radiation resulted in acceptable toxicity. Overall, the acute skin toxicity seen with docetaxel was more pronounced. However, among patients undergoing breast conservation the taxanes were both well tolerated. Further study is necessary to assess the impact of concurrent treatment on long-term outcome. **© 2000 Elsevier Science Inc.**

Paclitaxel, Docetaxel, Breast, Radiation.

INTRODUCTION

The taxanes (both paclitaxel and docetaxel) are rapidly gaining prominence in the management of solid tumors (1–5). The addition of these newer compounds to a doxorubicin regimen in the treatment of advanced breast cancer is under active investigation. A recent randomized trial reported by Henderson (6) showed a survival advantage in node-positive women who received sequential paclitaxel in addition to standard doxorubicin and cyclophosphamide chemotherapy. In high-risk breast cancer, the combination of concurrent paclitaxel and docetaxel chemotherapy with adjuvant radiation is an attractive alternative to sequential treatment, with potential for enhancing both local and systemic control. *In vitro* and *in vivo* evidence is accumulating that the taxanes act cooperatively with radiation, with additive or possibly even synergistic mechanisms (7, 8). Moreover, both retrospective and prospective studies have shown diminished local control when radiation therapy is delayed following definitive breast cancer surgery (9, 10). Because of the desire to incorporate a taxane in systemic management, the potential for diminished local control with delaying radiation, and the possible additive or even synergistic benefits of concurrent treatment, we began in 1995 to administer radiation therapy concurrently with the taxanes (first with paclitaxel, then with docetaxel) in advanced breast cancer. This preliminary reports examines the tolerance of such treatment.

METHODS AND MATERIALS

The records of 45 patients with high-risk breast cancer consecutively treated with radiation therapy and paclitaxel or docetaxel from January 1995 through March 1999 were reviewed. All patients were treated with curative intent or to maximize local control. Median follow-up was 11 months from the conclusion of radiation therapy (range 1 to 46 months). Forty-one patients were available for follow-up at 6 months, 22 at 12 months, 11 at 18 months, and 3 patients

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at 24 months. All patients gave written informed consent before beginning treatment, and were fully informed as to the nonstandard nature of this treatment.

Patients ranged in age from 27 to 70 years with median age of 51. Overall, patients had relatively few medical comorbidities with medical problems in 15 patients including hypertension (8 patients), coronary artery disease and myocardial infarction (3), diabetes mellitus (1), asthma (2), and history of rheumatic fever (1). Seven patients had received prior radiation for breast cancer. Two patients had received radiation for malignancies other than breast cancer, including one woman who had received mantle radiation for Hodgkin's disease, and another who had been treated with total body irradiation for acute myelogenous leukemia. Stage of disease ranged from I–IV. The majority of patients had either Stage IIIA or Stage IIIB disease (31%), or were treated at the time of recurrence (18 patients, 40%).

Radiation was delivered to the chest wall or breast with either tangential photon beams or electrons. Doses ranged from 4680 cGy to 5040 cGy for the patients who had not received prior radiation (median dose 5040 cGy). Doses for the 9 patients who had received prior radiation therapy ranged from 3000 cGy to 5280 cGy (median dose 4500 cGy). The majority of patients subsequently received a boost dose of radiation to the mastectomy incision, lumpectomy site, or site of recurrence. Thirty-seven patients (82%) were treated to the supraclavicular region, with 34 of these patients also receiving a posterior axillary boost. The internal mammary chain was also treated in 6 patients. For the 9 patients who had received prior radiation, the mean interval from the prior radiation to the current treatment was 4.9 years (range, 16 months to 14 years). All patients were treated with conventional fractionation except one who received a hyperfractionated schedule (120 cGy twice a day to 5280 cGy). Eleven patients were treated with the intent of breast conservation. Twenty-seven patients (60%) were treated with bolus over the breast or chest wall. This was utilized to minimize skin sparing in the postmastectomy setting and for patients with an intact breast and T4 disease.

Twenty-nine patients received concurrent paclitaxel alone, and 15 received concurrent docetaxel alone. One patient received both paclitaxel and docetaxel during the same course of radiation. The decision to give paclitaxel or docetaxel was based initially on drug availability and later, when both drugs were available, was at the discretion of the treating medical oncologist. Paclitaxel was given by protracted continuous infusion (20–35 $mg/m^2/d \times 4$ days (18 patients, 40%); median dose 35 $mg/m^2/d$) every 3 weeks or by rapid infusion every 3 weeks (135–175 mg/m^2 over 3 hours; median dose 175 mg/m^2; 9 patients, 20%). Docetaxel was administered every 3 weeks by 1-hour infusion (50–100 mg/m^2; median dose 60 mg/m^2) to 15 patients (33%). The patient treated with both drugs initially received docetaxel at 75 mg/m^2, but was later switched to short infusion paclitaxel (175 mg/m^2) due to docetaxel intolerance (agitation, insomnia). An additional 2 patients were treated with weekly paclitaxel. Two patients (one receiving paclitaxel and the other docetaxel) were also treated with concurrent vinorelbine. Most patients (98%) had received chemotherapy prior to the current regimen. For 42 (93%), this consisted of a doxorubicin-based regimen. While a variety of doxorubicin regimens were used, the majority received either conventional FAC (5-fluorouracil, doxorubicin, cyclophosphamide), or dose-intensive AC (doxorubicin, 24 mg/m^2 weekly, and oral cytoxan, 100 mg daily). A minimum interval of 3 weeks between the last administration of doxorubicin and the initiation of radiation was typically employed.

Table 1. Acute skin toxicity (Fisher's exact test)

	Grade 0–1	Grade 2	Grade 3	Total
Paclitaxel	10	16	3	29
Docetaxel	3	6	6	15
Total	13	22	9	44

$p = 0.04$ (Grade 0–2 vs. Grade 3).

Toxicity was assessed by the Radiation Therapy Oncology Group (RTOG) scale for acute and late effects. Number of days break from radiation therapy was also recorded, as was delay in administration of chemotherapy due to radiation toxicity. Fisher's exact test (2-sided) was used to compare the odds ratio of toxicity between regimens, and also to evaluate potential confounding factors contributing to toxicity. Analysis of variance (ANOVA) was also utilized to compare toxicity between different schedules of chemotherapy administration (11).

RESULTS

Overall, treatment was well tolerated. Nine patients (20%) experienced Grade 3 skin acute toxicity (confluent moist desquamation). Seventeen patients (38%) required a break in the course of radiation, with a median delay of 8 days. There were no Grade 4 or Grade 5 acute toxicities related to radiation therapy. In 5 patients (11%), acute radiation toxicity resulted in a delay in chemotherapy, with one or more cycles postponed until the conclusion of radiation treatments.

Three patients who received paclitaxel alone experienced a Grade 3 skin toxicity (10%), compared with 6 of 15 (40%) patients treated with concurrent docetaxel alone (Table 1). Of the 12 patients who required a break in the course of radiation of more than 5 days, 6 had received docetaxel, and 6 had received paclitaxel. Patients receiving paclitaxel were significantly less likely to experience a Grade 3 skin reaction than those receiving concurrent docetaxel ($p = 0.04$). However, when comparing those patients who did or did not require >5 days break from radiation due to toxicity, a significant difference between the two treatment regimens was not seen (6 of 29 paclitaxel patients compared with 6 of 15 docetaxel patients; p = nonsignificant [NS]).

Table 2. Acute skin toxicity (Fisher's exact test)

	Grade 0–2	Grade 3	*p* Value
Age <50	17	5	
Age ≥50	19	4	NS
Bolus +	18	9	
No bolus	16	0	0.02
Smoke +	10	4	
Nonsmoker	22	4	NS
Prior XRT	8	1	
No prior XRT	28	8	NS
Recurrent disease	15	3	
Primary disease	21	6	NS

Other factors potentially predictive of severe skin toxicity were also examined (Table 2). Only the use of tissue bolus to prevent skin-sparing resulted in statistically significant worse skin reaction. Patient age, smoking history, prior radiation, and treatment for recurrent disease were not predictive. Of note, patients receiving bolus were also more likely to have received docetaxel. Fifteen of 25 patients receiving paclitaxel were treated with tissue bolus compared with 10 of 15 patients who received docetaxel.

Among the 11 patients undergoing breast conservation (those with an intact breast, without prior radiation or inflammatory disease), 7 patients had a Grade 1 reaction, and 4 had Grade 2 reactions. Two of these patients were treated with concurrent docetaxel, and 9 with paclitaxel. There were no Grade 3 skin reactions, and no patient required a radiation treatment break longer than 5 days (2 patients required short breaks of 2 and 3 days, and the rest had no days off radiation secondary to toxicity).

The two predominant methods of paclitaxel administration, 96-hour continuous infusion and 3-hour infusion, were compared with each other and with the standard 1-hour infusion docetaxel regimen. On ANOVA analysis, no significant differences in number of days off due to acute toxicity were identified, likely due to the small numbers of patients in each subset.

One patient experienced long-term sequelae of concurrent treatment, with retraction, fibrosis, and telangiectasis of the breast. This was first noted at the time of a routine follow-up visit, 8 months after conclusion of treatment. She was the only patient who received 100 mg/m^2 of docetaxel. An additional patient who was treated with twice-daily radiation and concurrent paclitaxel for a chest wall recurrence developed acute pericarditis during treatment, necessitating premature cessation of her radiation treatment. This was managed with nonsteroidal anti-inflammatory medication, and hospitalization was not required. This patient had received prior radiation to the chest wall and regional lymphatics at the time of her initial presentation. There were no cases of either rib fracture, clinically significant pneumonitis, or brachial plexopathy.

DISCUSSION

Concurrent use of the taxanes and radiation therapy is gaining prominence in oncologic management. Paclitaxel has been successfully administered in the Phase I and II setting with various dosing schedules when given concurrently with radiation therapy to the head and neck (12), lung (13, 14), and brain (15). Docetaxel, while less well studied, has also been given concurrently with radiation therapy to the chest for non–small cell lung (16) and esophageal cancer (17), and to the bladder (18). One prospective, nonrandomized study from the University of Southern California (19) examined the role of concurrent paclitaxel and radiation therapy in the neoadjuvant setting for patients with locally advanced breast cancer. Paclitaxel was initially given weekly, at a dose of 60 mg/m^2; however, due to marked skin reaction, the dose was changed to 30 mg twice weekly, and the radiation reduced from a cumulative dose of 50 Gy in 25 fractions, to a cumulative dose of 45 Gy in 25 fractions. The altered regimen was well tolerated, with no Grade 3 skin reactions. Four of 8 evaluable patients achieved a pathologic complete or partial response. The authors conclude that concurrent treatment is both feasible (particularly at the amended dosing schedule) and promising.

The mechanisms by which radiation may interact with paclitaxel and docetaxel are not known. Paclitaxel has been shown to promote microtubule polymerization, inducing a G2/M block (20–22). It has been postulated that this promotes cell death by stalling cells in a radiation-sensitive phase of the cell cycle (20–23). The optimal schedule of chemotherapy and radiation necessary to maximize tumor cell kill is still to be determined. Talwar and Redpath found nonuniformity in degree of cell kill based on the schedule of radiation and drug administration (24). Maximum kill was seen when paclitaxel was given 10 hours after radiation exposure, and subadditive effects seen when paclitaxel was given immediately after radiation.

It may be the case that mechanisms other than G2/M delay contribute to the interaction between the taxanes and radiation. Recent work both in cell culture (25) and *in vivo* (26) has shown that paclitaxel induces apoptosis; and that apoptosis-induced cell death is more closely correlated with the antitumor property of paclitaxel than is mitotic delay (27). Whereas paclitaxel and docetaxel both result in microtubule stabilization, docetaxel has been shown to be more potent in its promotion of tubulin polymerization (28, 29). In HeLa cell culture, Hennequin *et al.* (30) have shown that docetaxel has specificity for cells in the radioresistant S-phase. Milas *et al.* (31) also postulated that paclitaxel may enhance radiation response by potentiating tumor reoxygenation. This was demonstrated in a murine mammary carcinoma model in which the tumor control dose for 50% of tumors (TCD50) was reduced and tumor growth delay increased in air-breathing as opposed to hypoxic conditions, and with a greater time interval from paclitaxel administration to radiation.

Concurrent administration of the taxanes and radiation is also attractive in that it permits both treatment modalities to be given without undue delay after surgery. Delay in the administration of radiation has been implicated in inferior local control rates. Buchholz (9) *et al.* reported the results of a retrospective review of 105 patients treated with surgery and adjuvant radiation therapy. Delay in radiation of greater than 6 months after surgery resulted in poorer local control (98% vs. 76%; $p = 0.004$), and overall survival ($p = 0.016$). Other retrospective reviews, however, have found no impact of delay in initiation of radiation therapy on local control (32, 33). In a prospective study of 244 patients with Stage I and II breast cancer randomized to radiation therapy before or after 12 weeks of chemotherapy, Recht found higher local recurrence rates in the radiation-delayed group (14% vs. 5% first site of recurrence), and higher distant metastatic rate in the group that received radiation first (10). Although the authors concluded that in patients at high risk for systemic recurrence it is preferable to give chemotherapy first, this is not without a price in terms of local control. This is likely to be even more significant with the extended chemotherapy regimens that patients with advanced breast cancer are now receiving. At our institution, patients with high-risk disease typically are treated with 12 weekly cycles of adriamycin and cyclophosphamide, followed by 4 cycles of a taxane. Postponing radiation therapy to the conclusion of all chemotherapy would frequently necessitate a 6-month delay.

Potential adverse outcomes related to prolongation of radiation therapy treatment time must, however, also be factored into any assessment of the overall benefit of concurrent treatment. Perez's large retrospective review of 1225 patients with Stage IB–III cervical carcinoma examines the impact of treatment duration on pelvic failure and cause-specific survival (34). Prolongation of overall treatment was associated with a 0.85% per day decrease in pelvic control. On multivariate analysis, overall treatment time was predictive of diminished local control in the pelvis, disease-free survival, and cause-specific survival. In an extensive 1992 review of 12 studies of definitive radiation therapy for head and neck cancer, Fowler and Lindstrom (35) also examined the impact of treatment duration on local control. Prolongation of treatment was found to diminish significantly the likelihood of local control, with a median decrease in the rate of local control of 14% per week. Eiffel and Thames warn that retrospective reviews are best interpreted with caution, as subtle confounding variables can affect both local control and length of treatment (36).

In conclusion, concurrent administration of the taxanes with radiation therapy in high-risk breast cancer is feasible. For breast conservation patients, concurrent treatment is particularly well tolerated, independent of the chemotherapy drug used. While numbers in each group are small, these patients had no Grade 3 toxicity, and minimal days break from radiation. Overall, toxicity from paclitaxel was less than that with docetaxel. However, this may also reflect imbalances in treatment groups. For example, patients receiving docetaxel were more likely to be treated with tissue bolus, which as expected, resulted in greater acute skin toxicity. In this group, mainly those patients who are postmastectomy and/or have T4 disease, potential benefits of concurrent treatment must be weighed against possible deleterious effects of unscheduled treatment breaks. Although the retrospective nature of this review coupled with the heterogeneity of patients and treatments limits the applicability of our results, this work can serve as a springboard for future prospective studies which can more specifically address issues such as optimal dose and timing. Further study is also required to assess the effect of concurrent treatment on local control and overall outcome.

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