Risk of Pneumonitis in Breast Cancer Patients Treated With Radiation Therapy and Combination Chemotherapy With Paclitaxel

Alphonse G. Taghian, Sherif I. Assaad, Andrej Niemierko, Irene Kuter, Jerry Younger, Robin Schoenthaler, Maria Roche, Simon N. Powell

Background: Some chemotherapy (CT) drugs, including taxanes, may enhance the effectiveness of radiation therapy (RT). However, combining these therapies may increase the incidence of radiation pneumonitis, a lung inflammation. In a retrospective cohort study, we evaluated the incidence of radiation pneumonitis in breast cancer patients treated with RT and standard adjuvant CT by use of doxorubicin (Adriamycin) and cyclophosphamide, with and without paclitaxel. Methods: Forty-one patients with breast cancer were treated with RT and adjuvant CT, including paclitaxel. Paclitaxel and RT (to breast–chest wall in all and lymph nodes in some) were delivered sequentially in 20 patients and concurrently in 21 patients. Paclitaxel was given weekly in some patients and every 3 weeks in other patients. The incidence of radiation pneumonitis was compared with that among patients in our database whose treatments did not include paclitaxel (n = 1286). The percentage of the lung volume irradiated was estimated. The Cox proportional hazards model was used to find covariates that may be associated with the observed outcomes. All P values were two-sided. Results: Radiation pneumonitis developed in six of the 41 patients. Three patients received paclitaxel concurrently with RT, and three received it sequentially (P = .95). The mean percentage of lung volume irradiated was 20% in patients who developed radiation pneumonitis and 22% in those who did not (P = .6). For patients treated with CT including paclitaxel, the crude rate of developing radiation pneumonitis was 14.6% (95% confidence interval [CI] = 5.6% to 29.2%). For patients treated with CT without paclitaxel, the crude rate of pneumonitis was 1.1% (95% CI = 0.2% to 2.3%). The difference between the crude rates with or without paclitaxel is highly statistically significant (P < .0001). The mean time to develop radiation pneumonitis in patients treated concurrently with RT and paclitaxel was statistically significantly shorter in patients receiving paclitaxel weekly than in those receiving it every 3 weeks (P = .002). Conclusions: The use of paclitaxel and RT in the primary treatment of breast cancer should be undertaken with caution. Clinical trials with the use of combination CT, including paclitaxel plus RT, whether concurrent or sequential, must evaluate carefully the incidence of radiation pneumonitis. [J Natl Cancer Inst 2001;93:1806–11]

The use of adjuvant therapy for patients with stage I or stage II breast cancer is well established. In an attempt to improve the outcome, several strategies have been evaluated, one of which is the incorporation of taxanes into adjuvant chemotherapy (CT) regimens. Taxanes have been found to be important drugs in the treatment of metastatic breast cancer (1). For patients with positive lymph nodes, preliminary data suggested that the addition of paclitaxel to standard adjuvant CT might improve the outcome (2). Although the currently available data are inconclusive and do not permit definitive recommendations regarding the impact of taxanes on either disease-free survival or overall survival (3), adjuvant CT with the use of four cycles of a doxorubicin (Adria- mycin)–cyclophosphamide combination followed by paclitaxel is commonly used in the United States for patients with positive axillary lymph nodes (3).

It is known that certain chemotherapeutic agents have a synergistic interaction when given concurrently with radiation therapy (RT) (4). Paclitaxel has been shown to enhance the effect of RT in vitro (5) and in vivo through different mechanisms (6–8). Taxanes were also found to increase the cytotoxicity of RT on normal tissue in an animal model (9,10).

Since the optimal dose and delivery schedule of paclitaxel therapy for breast cancer have not yet been defined, one can assume that it might be beneficial to treat these patients with paclitaxel and RT concurrently. This has the advantage of delivering RT without delay, which might improve local control (11) while still allowing completion of CT in a timely fashion.

Radiation pneumonitis is usually a rare complication, which increases with the use of CT (12). The overall reported incidence of radiation pneumonitis in patients treated for breast cancer with or without CT varies between 1% and 16% (13–15). Several factors play a role in increasing its rate, among them the total dose, fractionation of radiation, the volume of lung irradiated, and the use of chemotherapeutic drugs, especially if given concomitantly with RT (12,16).

Here, we report the rate of radiation pneumonitis in patients with breast cancer and positive lymph nodes who received paclitaxel as part of their adjuvant CT, either concomitantly or sequentially, with breast irradiation. The RT dose, radiation technique used, and lung volume irradiated were assessed and compared between patients who received paclitaxel sequentially and concurrently and between those who developed radiation pneumonitis.

Subjects and Methods

Patient Population

This is a retrospective report, including 41 patients with breast cancer who received paclitaxel as part of their adjuvant CT (38 patients) or neoadjuvant CT (three patients). All patients gave written informed consent before starting the treatment, and those who received concurrent paclitaxel with RT were informed about the nonstandard nature of the therapy. The patients were treated from 1993 through 1999, with 31 (76%) patients treated from 1997 through 1998. This group represents all patients treated by combination CT with paclitaxel and RT at our institution during this period. The median age for these patients was 49 years (range, 25–73 years). All patients received doxorubicin-based CT in addition to paclitaxel treatment. Paclitaxel and RT were delivered sequentially in 20 patients and concurrently in 21. Of the 20 patients who received paclitaxel sequentially with RT, 15 were treated every 3 weeks at a dose of 175 mg/m²; five were treated weekly at a dose of 70–80 mg/m². Patients received RT after completing all CT. Among 21 patients who received paclitaxel concurrently along with RT, seven were given paclitaxel every 3 weeks.

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Patients Treated Without Paclitaxel

To evaluate the increase in incidence of radiation pneumonitis associated with exposure to paclitaxel in this series, we analyzed the incidence of pneumonitis in female patients in our database who did not receive paclitaxel as part of their treatment. From 1982 through 1995, a total of 1286 patients with breast cancer received RT as part of their treatment. Of these patients, 849 received RT only with no CT and 437 received RT and CT without paclitaxel. The median age of the patients in these subgroups was 64 years (range, 28–88 years) and 52 years (range, 26–83 years), respectively. The median follow-up time was 7 years. In the patients who received RT only and RT plus CT with no paclitaxel, the RT was given to the breast–chest wall alone in 569 and 157 patients, respectively, and to regional lymph nodes in 280 and 280 patients, respectively. The routine follow-up of these patients was similar to the group who received paclitaxel.

Sequential Versus Concurrent Paclitaxel With RT

To evaluate the effect of the sequential treatment of paclitaxel with RT in the development of radiation pneumonitis, we compared the doses and fields of RT and the volume of lungs irradiated in the group of patients who received sequential versus concurrent paclitaxel with RT and developed radiation pneumonitis (Table 2).

Volume of Lung Irradiated

To give an estimate of the volume of lung irradiated, we calculated the central lung distance (CLD) from direct measurement from the simulation films and we used the model described by Das et al. (17). This model estimates 0.6% of lung volume per mm CLD for the left lung and 0.5%/mm for the right lung. When the supravacular field was used, we added 12% to the irradiated lung volume, dependent on the simulation field (17).

Radiation Pneumonitis

All patients with radiation pneumonitis in this series were diagnosed and graded as stage 2–3 according to the Radiation Therapy Oncology Group (RTOG) Acute Morbidity Scoring Criteria (18).

Statistical Methods

For patients treated with paclitaxel, the rate of radiation pneumonitis was calculated as a 1-year actuarial rate by use of the product-limit method as well as a crude rate. In our dataset, these two methods gave very similar results because the mean and the median follow-up times (704 and 586 days, respectively) are significantly longer than the mean time to develop pneumonitis (59 days). We used the actuarial methods, because five patients were followed for a shorter time than the longest time to develop pneumonitis (122 days). For patients treated without paclitaxel, we used the crude rate method because the median follow-up was much longer (7 years), and the number of patients with relatively short follow-up times was negligible. For the actuarial analysis, the patients were censored at the time of follow-up or at the time that they died. For the calculation of 95% confidence intervals (CIs) around the survivor function, we used the asymptotic variance of ln (−ln) of the survivor function. To compare proportions, we used a standard two-sample test of proportions with a continuity correction. The 95% CI for the crude rate was calculated as an exact binomial interval. We used the two-sample Student’s t test to compare continuous data in two independent groups. The Cox proportional hazards model was used to analyze the paclitaxel data to find covariates (the use of standard CT with or without paclitaxel, the number of radiation fields, the dose used in the tangent fields, and the fractionation of RT) that may be associated with the observed outcomes. All statistical tests were two-sided. A P value of <.05 was considered to be statistically significant.

Results

Of the 41 patients who received paclitaxel as part of their CT regimen, six developed clinical–radiologic evidence of radiation pneumonitis (Table 3). These patients presented with a severe dry cough that was unresponsive to narcotic antitussive agents, dyspnea, and radiologic evidence of acute pneumonitis. Five of them (RTOG score 3) required steroids, and one (RTOG score 2) did not. The 1-year actuarial rate was 15.4% (95% CI = 7.2% to 31.1%). Table 3 describes the treatment received by these patients. The mean time from the end of RT to the development of radiation pneumonitis was about 8 weeks (range, 1 week to 4 months). Three of the six patients received concurrent paclitaxel; the other three received sequential paclitaxel with an actuarial incidence of 14.3% (95% CI = 4.8% to 38.0%) and 16.4% (95% CI = 5.6% to 42.7%), respectively (P = .87). Two of the three patients who received concurrent paclitaxel and developed radia-

Table 1. Description of the dose of paclitaxel chemotherapy, radiation fields, and percentage of lung volume irradiated (A) and doses and different radiation fields (B) in breast cancer patients who received paclitaxel sequentially or concurrently with radiation therapy*
Table 2. Difference in doses, fields of radiation, and volume of lungs irradiated in the groups of breast cancer patients who received paclitaxel sequentially or concurrently with radiation therapy and developed radiation pneumonitis

<table>
<thead>
<tr>
<th>Radiation pneumonitis</th>
<th>Sequential therapy</th>
<th>Concurrent therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radiation* pneumonitis</td>
<td>No radiation* pneumonitis</td>
</tr>
<tr>
<td>No. of patients</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Dose to the tangents, Gγ</td>
<td>48.6</td>
<td>48.4</td>
</tr>
<tr>
<td>Dose to supraclavicular, Gγ</td>
<td>50</td>
<td>47.5</td>
</tr>
<tr>
<td>Dose to the axilla, Gγ</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>Central lung distance, cm</td>
<td>2.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Lung volume irradiated, %</td>
<td>26.3</td>
<td>21.3</td>
</tr>
</tbody>
</table>

*None of the differences were statistically significant in the Cox proportional hazards analysis.

diation pneumonitis were treated with a weekly regimen at doses of 80 and 90 mg/m². One patient received paclitaxel on a 3-week regimen at a dose of 175 mg/m². All three patients who received sequential paclitaxel–RT and developed radiation pneumonitis were on a 3-week regimen at a dose of 175 mg/m².

Four of the six patients who developed radiation pneumonitis (Table 3) received RT to the breast–chest wall and regional lymph nodes. One patient received RT to the breast and an independent field to the internal mammary lymph nodes, and one received RT to the breast and internal mammary lymph nodes through wide tangents. The doses used ranged between 40 and 50 Gy, with a mean of 45 Gy and a boost to the tumor bed in lumpectomy patients varying between 16 and 20 Gy. The regional lymph node areas received a total dose ranging from 43.2 Gy to 56.4 Gy, with a mean of 48 Gy. Of the 25 patients (15 with concurrent and 10 with sequential treatment) who received RT at wide tangents, three (12%) patients (one with concurrent and two with sequential treatment) developed radiation pneumonitis compared with three (19%) (two with concurrent and one with sequential treatment) of 16 (six with concurrent and 10 with sequential treatment) who received radiation to the internal mammary chain through an independent electron field (P = .66).

The mean percentage of lung volume irradiated in the radiation pneumonitis patients versus that in the nonpneumonitis patients was 20% versus 22%, respectively (P = .6). However, the mean percentage of lung volume irradiated (26.3%) in three patients who developed radiation pneumonias after receiving RT and paclitaxel treatment sequentially was larger than the mean percentage value (14%) in the other three radiation pneumonitis patients receiving concurrent RT and paclitaxel treatment, although this difference was of borderline statistical significance (P = .06). It should also be noted that the doses of RT used in patients treated concurrently were statistically significantly lower (P<.0001) than the doses used in the group receiving sequential treatment (Table 1).

Increased Incidence of Radiation Pneumonitis

In our institution, the crude rate of radiation pneumonitis in patients treated with RT for breast cancer was 1.0% (95% CI = 0.5% to 1.7%) and was essentially the same as the actuarial rate. The incidence of radiation pneumonitis in the RT-only group was 1.1% (95% CI = 0.4% to 2%) and in the RT–CT group (no paclitaxel) was 0.9% (95% CI = 0.2% to 2.3%) (Fig. 1). The actuarial and crude rates of radiation pneumonitis in patients who were treated with RT and CT including paclitaxel were 15.4% (95% CI = 7.2% to 31.1%) and 14.6% (95% CI = 5.6% to 29.2%), respectively. This difference was statistically highly significant (P<.0001).

Time Interval to Develop Radiation Pneumonitis

The mean time from the end of RT to the development of pneumonitis in patients who developed radiation pneumonitis in the nonpaclitaxel group was 5 months (range, 10 days to 17 months) compared with 1.9 months in the paclitaxel group (range, 1 week to 4 months) (P = .01). The mean time intervals in

Table 3. Details of the treatments delivered to the breast cancer patients who received chemotherapy, including paclitaxel and radiation therapy, and developed radiation pneumonitis*

<table>
<thead>
<tr>
<th>Radiation therapy</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>Tangents, Dx/fr</td>
</tr>
<tr>
<td>1</td>
<td>MRM</td>
</tr>
<tr>
<td>2†</td>
<td>Lump</td>
</tr>
<tr>
<td>3</td>
<td>Lump</td>
</tr>
<tr>
<td>4</td>
<td>Lump</td>
</tr>
<tr>
<td>5</td>
<td>Lump</td>
</tr>
<tr>
<td>6</td>
<td>Lump</td>
</tr>
</tbody>
</table>

*Dx/fr = dose per fraction; IMC = internal mammary lymph nodes field; lump = lumpectomy; S/C = supraclavicular; CLD = central lung distance measured on the simulation film; CT = chemotherapy; MRM = modified radical mastectomy; CAF = cyclophosphamide/doxorubicin (Adriamycin)/5-fluorouracil; Conc. = concurrent; AC = doxorubicin (Adriamycin)/cyclophosphamide; boost = radiation dose to the tumor bed after whole-breast irradiation; Seq. = sequential; A = doxorubicin (Adriamycin); T = paclitaxel.
†This patient presented with dyspnea on exertion, and the chest x-ray showed infiltrates. The patient did not receive prednisone.
‡Patients received the internal mammary lymph node radiation therapy through wide tangents.
§The patient received a 6-Gy boost to the axilla.
| Patients received a 18-Gy boost because of focally positive margins. |
patients who developed pneumonitis in the concomitant (three patients) versus sequential (three patients) RT–paclitaxel groups were 51 days (range, 7–122 days) and 67 days (range, 49–83 days), respectively. However, the mean time to develop radiation pneumonitis in patients who received weekly paclitaxel was 16 days (range, 7–23 days) versus 81 days (range, 49–122 days) for those receiving the 3-week regimen ($P = .002$).

**Cox Proportional Hazards Analysis of Radiation Pneumonitis**

In the paclitaxel group, none of the analyzed parameters (the dose to the tangents, the dose to the supraclavicular area, the dose to the axilla, the CLD, the percentage of lung volume irradiated, the number of radiation fields, age, and the sequential or concurrent administration of paclitaxel with RT) was significantly associated with the observed outcome (Table 2).

**Treatment Outcome**

Five patients (two with concurrent therapy and three with sequential therapy) of the six patients required prednisone therapy (1 mg/kg of body weight) for various periods of time varying between 1.5 and 11 weeks, before clinical and radiologic improvement. All of the patients were treated successfully.

**DISCUSSION**

The potential advantages of combining RT and CT for local and distant control of breast cancer may be offset by increased toxicity. Several studies (12,14,19) have suggested that women who are treated with both RT and CT have a higher risk of toxic reactions, including radiation pneumonitis. The results of our study show that, in breast cancer patients, administration of paclitaxel, whether sequentially or concurrently with RT, after standard doxorubicin-based CT may be associated with an increased risk of radiation pneumonitis. This risk was found to be above that for patients who are given CT without paclitaxel ($P = .0001$). In our database, the rate of radiation pneumonitis in patients who received RT alone without CT was 1.1%. This rate did not increase in patients who received RT and CT that did not include paclitaxel. In contrast, Lingos et al. (12) found that the risk of radiation pneumonitis in patients who received CT (without paclitaxel) increased from 0.2% to 0.6% for RT alone to 3.3% for sequential and 8.8% for concurrent RT (three fields) with CT. In our study, adding paclitaxel increased the risk of radiation pneumonitis from 1% to 16.2% ($P = .0001$).

**Radiation Pneumonitis in Concurrent Paclitaxel and RT**

In this series, the actuarial rate of radiation pneumonitis in patients who received concurrent paclitaxel and RT was 14.3%. Hanna et al. (20) described a series of 20 patients treated with four cycles of doxorubicin–cyclophosphamide followed by concurrent paclitaxel and RT similar to the patients in our series. Most patients received doses varying between 50.4 and 54.0 Gy. The authors reported a 25% risk of radiation pneumonitis; two of these five patients required hospitalization. The authors also found a grade II or higher skin toxicity in 12 patients. In this series, with the use of the RTOG score, we did not encounter an increase in skin toxicity in patients who received concomitant paclitaxel and RT (data not shown). This result is in contrast with the findings from other studies (21–23). Bellon et al. (21) reported on 29 patients, the majority of whom received doses between 46.8 and 50.4 Gy. All of these patients were treated with concurrent paclitaxel, and 19 of them presented with grade 2 or 3 (RTOG scale) acute skin toxicity. However, Bellon et al. did not report any cases of pneumonitis. On the other hand, Skinner et al. (23) and Formenti et al. (22) reported their experience in 27 assessable patients with locally advanced breast cancer treated by neoadjuvant concomitant paclitaxel and RT followed by modified radical mastectomy in most of them. Initially, the study by Formenti (22) was designed with patients receiving paclitaxel at a dose of 60 mg/m² per week and comprehensive RT at a total dose of 50 Gy. Because the first two patients experienced severe unusual chest wall skin reaction requiring flap reconstruction, the dose of paclitaxel was modified into twice-weekly administration at a dose of 30 mg/m² and a RT dose of 45 Gy (22). There was no reported radiation pneumonitis in this series.

In our series, lower doses of RT were used in the group of patients treated concurrently with paclitaxel, which varied between 40 and 46 Gy (average, 42 Gy; see Table 1). In addition, the percentage of lung volume irradiated in the patients who developed radiation pneumonitis in the group receiving RT and paclitaxel concurrently was only 14% compared with 26.3% in the group receiving sequential RT and paclitaxel treatment. In those patients without radiation pneumonitis, approximately 22% of the lung volume were irradiated in both groups. These findings raise the possibility that, with concurrent therapy, reduction in the volume of the lung irradiated does not necessarily offset the risk of radiation pneumonitis. Furthermore, it leaves paclitaxel as the dominant risk factor for the development of radiation pneumonitis. It is interesting to note that weekly administration was associated with early presentation with radiation pneumonitis in our series as well as in the series of Hanna et al. (20).

![Fig. 1. Crude rate of radiation pneumonitis in patients with breast cancer treated by surgery followed by radiation therapy (RT) alone, RT with chemotherapy (CT) not including paclitaxel, or RT with CT including paclitaxel. The rate of radiation pneumonitis was calculated at different time intervals. The error bars indicate the 95% confidence intervals.](image-url)
Radiation Pneumonitis in Sequential Paclitaxel and RT

Our study also showed an actuarial rate of radiation pneumonitis of 16.4% in patients who received sequential paclitaxel and RT. Because this population included mostly high-risk patients, the majority (15 of 20) had all of their regional lymph nodes irradiated (Table 1, A), and all patients had their internal mammary lymph nodes irradiated (five patients through wide tangents). By contrast, in the Cancer and Leukemia group B study (CALGB 93–44), patients with positive lymph nodes were treated with adjuvant CT with the use of four cycles of doxorubicin–cyclophosphamide with or without paclitaxel (2). The regional lymph node irradiation was left to the discretion of the treating physician. The interim analysis (median follow-up, 21 months) showed a statistically significant reduction in death rate by 26% with the addition of paclitaxel (2). In this report, the authors did not mention an increase in lung toxicity related to the addition of paclitaxel. A similar study from the National Surgical Adjuvant Breast Project (NSABP B-28) has shown no difference in disease-free survival or in overall survival by adding paclitaxel (3). Regional lymph node irradiation was not recommended in this study. The interim analysis at a median follow-up of 34 months did not mention an increase in radiation pneumonitis by adding paclitaxel (3). The reason for the discrepancy between these two studies and ours is unclear. One possibility is that toxicity was underreported in these multi-institutional trials. It is also possible that, because most patients in our series received regional RT, the volume of the lung irradiated could be larger than the volume irradiated in these two randomized studies. However, this volume is considered to be within the normal range used in four fields’ irradiation (RT to cover the breast–chest wall and the regional lymph nodes areas) and equivalent to that used in patients treated without paclitaxel.

Other Factors in Treatment-Induced Pneumonitis

It is noteworthy to mention the possibility of paclitaxel-induced pneumonitis with no use of RT. There have been several cases reported with early or delayed onset (24–26). It has also been suggested that the rapid withdrawal of steroids may result in a flare-up radiation pneumonitis, regardless of the time interval between the lung irradiation and acute withdrawal (27,28). When paclitaxel is used, prophylactic dexamethasone is commonly given before paclitaxel administration, to minimize any hypersensitivity reaction to the Cremophor. It is possible that both factors have played a role in the increased risk of radiation pneumonitis.

In conclusion, although the number of patients in this series is relatively small, these data suggest that paclitaxel has a statistically significant enhancing effect on the toxicity of RT to the lung. Concomitant paclitaxel and RT resulted in an actuarial risk of radiation pneumonitis (14.3%) similar to that seen with sequential therapy (16.4%). Therefore, in the absence of clear benefit from adding paclitaxel to four cycles of doxorubicin–cyclophosphamide, the potential toxicity should be carefully considered before use of this drug is recommended in the adjuvant setting. Clinical trials should also monitor accurately the extent of lung included within the RT volume to develop safe guidelines for the delivery of this frequently used therapy for lymph node-positive breast cancer.

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