Paclitaxel Enhances in Vitro Radiosensitivity of Squamous Carcinoma Cell Lines of the Head and Neck1

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ABSTRACT

Squamous cell carcinoma of the head and neck is the fourth most common cancer in the United States, and therapy for very advanced cases is relatively ineffective. Paclitaxel has activity against cancers of the breast, lung, prostate, cervix, and ovary. The activity of paclitaxel for squamous cell carcinoma of the head and neck is less certain, and results of its radiosensitization properties have been variable.

The radiation responses of two squamous carcinomas, SCC-9 (oropharynx) and HEP-2 (larynx), were examined to determine the radiosensitizing potential of paclitaxel. In vitro exposures for 24 and 48 h with paclitaxel concentrations of $10^{-4}$ to $6 \times 10^{-2}$ μg/ml were followed by irradiation of 0.1–10 Gy. Percent survival was calculated by colony count, and the paclitaxel-radiation interaction was quantitated by the median effect principle and the combination index method of Chou and Talalay.

The paclitaxel-radiation combination resulted in multiphasic interactions in both 24 and 48 h paclitaxel pretreatment in SCC-9 and HEP-2 cell lines. In general there was slight synergism [combination index (CI) <1] at low dose-low effect levels (e.g., at a paclitaxel concentration of 0.002 μg/ml or lower and radiation of 0.1–0.3 Gy), moderate antagonism (CI >1) at medium dose ranges and strong synergism (CI <1) at high dose ranges (e.g., at a paclitaxel concentration of 0.012–0.06 μg/ml and radiation doses of 3–10 Gy), especially at a surviving fraction of <0.1, which is therapeutically relevant.

The median effect principle and combination index method provided a simple way to quantify the synergism or antagonism of a paclitaxel-radiation interaction under various conditions. This analysis demonstrated that paclitaxel-radiation synergy exists at doses that are readily achievable in the clinical scenario for both agents and that greater synergy occurred at high dose-high effect levels. These results suggest that the combination of both therapies should be explored further in clinical trials assessing the treatment of squamous cell carcinomas of the head and neck.

INTRODUCTION

In the United States, paclitaxel has been approved for use in human ovarian cancer (1, 2) and breast cancer (3). The role of paclitaxel in the treatment of squamous cell carcinomas of the head and neck and other organs is less well defined in the clinic, although there is some evidence of moderate activity (4–6). Paclitaxel overstabilizes microtubule formation and may enhance radiosensitivity by blocking these cells in the most sensitive phases of the cell cycle, G2 and M (7). If more cells are arrested in these phases of the cycle, then radiation should be more efficient in its cytotoxic effects. Therefore, in addition to the additive effects of cell killing secondary to either radiation or paclitaxel alone, there may be an additional population of affected cells that otherwise may have been spared.

The role of paclitaxel as a radiosensitizer has been variable with both positive and negative studies (8–20). These differences may be attributable to the type of cells examined or other technical and analytical variations. Paclitaxel has been reported to enhance the in vitro radiosensitivity of human ovarian, astrocytoma, leukemia, cervical, breast, and prostate carcinoma cell lines. However, other studies have not shown that paclitaxel has any radiosensitization effect in colon or lung carcinoma cell lines (12, 15). There also have been conflicting or equivocal results of paclitaxel radiosensitization in pancreatic, prostate, breast, and cervical carcinoma cell lines (12, 15–17). Currently, little quantitative research has addressed whether paclitaxel enhances the radiosensitivity of squamous cell carcinoma of the head and neck (20) and, if so, whether this effect is synergistic or merely additive.

The work presented in this paper investigates the in vitro activity of paclitaxel alone and as well as its effect in combination with radiation against two squamous cell carcinomas of the head and neck, SCC-9 and HEP-2. The combined effect of the two modalities was analyzed by the median effect principle and CI3 method of Chou and Talalay (21) and others (22–26).

MATERIALS AND METHODS

Cell Culture. SCC-9 and HEP-2 cell lines were obtained from the American Type Culture Collection (Rockville, MD). Both of these cell lines are derived from squamous cell carcinomas of the head and neck (SCC-9 from oropharynx and HEP-2 from larynx). The cells were grown in DMEM containing 0.4 μg/ml hydrocortisone, 100 units/ml penicillin, 100 μg/ml streptomycin, and 10% fetal bovine serum and maintained at 37°C and 5% CO2.

Paclitaxel Solution. Paclitaxel was obtained from Bristol-Myers Squibb (Princeton, NJ) freshly dissolved in DMSO and further diluted at the appropriate concentration in the medium.

Treatment of Cells with Paclitaxel. Eight hundred cells were plated in 35-mm tissue culture dishes in triplicate (single-cell suspension), and various concentrations of paclitaxel (1 × $10^{-4}$ to $6 \times 10^{-2}$ μg/ml) were added 24 h after the medium had been changed, cells were incubated for approximately 2–3 weeks for colonies to establish. Colonies were fixed with 2% acetic acid and 8% ethanol and then stained with propidium iodide for cell cycle analysis using the method of Modfit (Verity Software House, Topsham, ME). At least two or three complete experiments were performed for each experimental regimen.

Cell Cycle Analysis. SCC-9 and HEP-2 cells were treated with various concentrations of paclitaxel for 1, 6, 12, 24, and 48 h. Single-cell suspensions were stained with propidium iodide for cell cycle analysis using the method of Krishan (27). Flow cytometry was performed on a Coulter Epic 752 flow cytometer. Data for 20,000 events were collected with a Cicero Data Acquisition System using Cytomine Software (Cytomation, Fort Collins, CO). Integrated red fluorescence versus peak red fluorescence gating was used for doublet discrimination. Modfit (Verity Software House, Topsham, ME) was used for cell cycle analysis.

TREATMENT OF CELLS WITH RADIATION. Eight hundred cells were plated in 35-mm tissue culture dishes in triplicate and irradiated 48 h later in various single radiation doses using a Varian 6 MV linear accelerator (Varian, Palo Alto, CA) at a source-to-target distance of 80 cm. The medium was changed 24 h after radiation and incubated for approximately 2 weeks to allow colonies to grow.
to form. The colonies were fixed, stained, and counted as described above. These experiments were repeated at least two or three times.

**Combined Treatment of Cells with Radiation and Paclitaxel.** Eight hundred cells were plated in triplicate, and various concentrations of paclitaxel (1 × 10^{-4} to 6 × 10^{-2} μg/ml) were added 24 h later. The medium with paclitaxel was changed after 24- and 48-h exposure times for the SCC-9 cell line and 48 h for the HEP-2 cell line. Subsequently, cells were irradiated at various radiation doses and incubated for 2–3 weeks to allow colonies to form. The colonies were fixed, stained, and counted as described above. Each complete experimental regimen was repeated at least twice.

**Determination of Synergism and Antagonism and the Construction of Isobolograms.** The CI was calculated by the Chou-Talalay equation, which takes into account both the potency (Dₐ₅₀ or ICₕ₀) and the shape of the dose-effect curve (the m value;Refs. 21–23). The general equation for the classic isobologram (CI = 1) is given by:

$$CI = \frac{(D_1)_{CI} + (D_2)_{CI}}{(D_1)_{CI} + (D_2)_{CI}}$$

(A)

where (Dₐ₅₀) and (Dₐₕ₀) in the denominators are the doses (or concentrations) for Dₐ (paclitaxel) and Dₙ (radiation) alone that give x% inhibition, whereas (Dₐ) and (Dₙ) in the numerators are the doses of taxol and radiation in combination that also inhibit x% (i.e., isoeffectual). CI < 1, CI = 1, and CI > 1 indicate synergism, additive effect, and antagonism, respectively.

The (Dₐ₅₀) or (Dₐₕ₀) (for paclitaxel or radiation) can be readily calculated from the median-effect equation of Chou (23) and Chou et al. (24):

$$D_a = \frac{f}{1 - f}$$

(B)

where Dₐ is the median-effect dose that is obtained from the anti-log of the X-intercept of the median-effect plot, X-log (D) versus Y = log(f/(1-f)), or Dₐ = 10^{-X Intercept/m}, and m is the slope of the median-effect plot. Computer software of Chou and Chou (25, 26) allows automated calculation of m, Dₐ, and CI values. From (Dₐ₁), (Dₐ₂), and (Dₐ₁ + Dₐ₂), it becomes easy to construct isobolograms automatically based on Eq. A (21, 25).

For conservative mutually nonexclusive isobolograms of two agents, a third term,

$$\frac{(D_1)(D_2)}{(D_1)_{CI}(D_2)_{CI}}$$

(C)

is added to Eq. A (21, 23).

For simplicity, the third term is usually omitted, and thus the mutually exclusive assumption or classic isobologram is indicated (21, 23). In Tables 1–3, the CI values obtained from the classic (mutually exclusive) calculation are given.

**RESULTS**

**Treatment of Cells with Paclitaxel and Radiation Alone.** Survival curves for the SCC-9 cell line after 24- and 48-h treatment with paclitaxel alone are shown in Fig. 1A. After an exposure time of 48 h, there was significantly more toxicity than after a 24-h exposure. Cells incubated with the same concentration of DMSO were not affected (data not shown). Fig. 1B shows the effect of paclitaxel on cell cycle distribution with SCC-9 cells. The 6- and 12-h exposures did not result in any substantial percentage of increase of cells in G₂-M arrest in SCC-9 cells. However, both 24- and 48-h paclitaxel treatment result in a substantial G₂-M accumulation that occurred at a concentration of 0.001 μg/ml and reached a maximum of 52% at 0.3 μg/ml with a 48-h exposure and 46% at 0.03 μg/ml with a 24-h exposure. Our cell cytometry data confirmed an increase in G₂-M as well as a sub-G₁ population as exposure times increased for each concentration of paclitaxel (0.001, 0.01, and 0.1 μg/ml; Fig. 1C). For each paclitaxel concentration, increasing exposure times results in a simultaneous increase in a G₂-M as well as a sub-G₁ population (suggesting a simultaneous increase in an apoptotic population).

A survival curve similar to the SCC-9 cell line was obtained for the paclitaxel cell line after a 48-h paclitaxel exposure (Fig. 2A). Again, HEP-2 cells incubated with the same concentrations of DMSO were not affected (data not shown). HEP-2 cells also showed a substantial G₂-M accumulation starting at 0.006 μg/ml of paclitaxel with 24- and 48-h exposures (Fig. 2B). However, in contrast to the SCC-9 cell line, 6- and 12-h exposures produced notable (yet smaller) increases of cells in G₂-M phase. A maximum G₂-M arrest occurred at 0.03–0.06 μg/ml of paclitaxel. Fig. 2C illustrates the cell cytometry data of increasing exposure times and concentration of paclitaxel for the HEP-2 cell line. As noted in the SCC-9 cell line, a similar pattern of increasing G₂-M and sub-G₁ populations occurs with increasing exposure times of each concentration of paclitaxel. Comparatively, the G₂-M and sub-G₁ populations were slightly larger for each exposure time/paclitaxel concentration than those seen for the SCC-9 cell line.

Fig. 3 shows the log-logistic plot of radiation survival curves for the SCC-9 and HEP-2 cell lines. When displayed in a semilogarithmic fashion (data not shown), both cell lines exhibited a broad initial shoulder in the radiation doses we examined.

**Treatment of Cells with Both Radiation and Paclitaxel.** Fig. 4, A and B, illustrates the cell survival curve of the SCC-9 cell line after 24- and 48-h paclitaxel exposure followed by various radiation doses. Fig. 5 illustrates the cell survival curve of the HEP-2 cell line after a 48-h paclitaxel exposure combined with radiation. Figs. 4 and 5 again illustrate cell survival curves with an initial shoulder similar to radiation alone (although slightly lower). Increasing concentrations of

**Table 1. Mutually exclusive CIs for the combination of radiation and a 24-h paclitaxel pretreatment at various dose and effect levels in SCC-9 cells**

<table>
<thead>
<tr>
<th>Concentration of paclitaxel (μg/ml)</th>
<th>CI at radiation level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.002</td>
<td>0.654⁵, 0.663⁶</td>
</tr>
<tr>
<td>0.006</td>
<td>1.154, 1.187</td>
</tr>
<tr>
<td>0.012</td>
<td>1.497, 1.625</td>
</tr>
<tr>
<td>0.06</td>
<td>0.615⁵, 0.475⁵</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concentration of radiation (Gy)</th>
<th>CI at radiation level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 Gy</td>
<td>0.732⁶, 0.953⁶, 1.402, 1.938</td>
</tr>
<tr>
<td>0.3 Gy</td>
<td>1.000, 1.261</td>
</tr>
<tr>
<td>1 Gy</td>
<td>1.059, 1.011</td>
</tr>
<tr>
<td>3 Gy</td>
<td>0.920⁵, 0.783⁵</td>
</tr>
<tr>
<td>6 Gy</td>
<td>0.584⁵, 0.511⁵</td>
</tr>
</tbody>
</table>

a Dose levels at which the CI is less than 1, indicating synergism.

b Synergism in the mutually exclusive interaction and lack of synergism in the mutually nonexclusive interaction.
PACLITAXEL RADIOSENSITIZATION OF SQUAMOUS CELL CARCINOMA

paclitaxel result in a smaller percentage survival for each dose of radiation (illustrated by the downward shift of the survival curves). This is even more pronounced for the intermediate paclitaxel concentrations in the SCC-9 48-h exposure compared to the 24-h exposure.

Table 1 illustrates the mutually exclusive CIs when the SCC-9 cell line is treated for 24 h with increasing concentrations of paclitaxel and doses of radiation. These results show a multiphasic distribution of synergism. The highest dose range of each modality (regardless of the dose of the other modality) results in strong synergy. CI values are much less than 1, denoting the highest synergism of paclitaxel and radiation together. The smallest concentration of paclitaxel (0.002 µg/ml) with the lowest radiation dose (0.1 Gy) results in weak synergism. The greatest degree of synergism (smallest CI value, 0.065) results from an exposure of 0.012 µg/ml of paclitaxel and 10 Gy of radiation. This coincides with the lowest concentration of paclitaxel, at which we noted an increase in the percentage of cells blocked in the G2-M phases of the cell cycle (but not the greatest G2-M arrest). Although the mutually exclusive CI value for 0.002 µg/ml of paclitaxel and 0.3 Gy of radiation shows weak synergy (0.863), a more conservative analysis only results in an additive interaction at best (a mutually nonexclusive CI value of 1.031).

Table 2 illustrates the SCC-9 cell survival after a combination of radiation and 48 h of paclitaxel exposure. Again, a multiphasic interaction is evident. CI values are much less than 1 in the high-dose range of both modalities, denoting the greatest synergism, and the moderate doses result in higher CI values (although less than 1), indicating a weaker synergy. As in the results of the 24-h exposure, the lowest CI values (indicating the greatest synergism) are at a paclitaxel concentration of 0.012 µg/ml and appear to gradually decrease (denoting increased synergism) with increasing doses of radiation. A radiation dose of 6 Gy and 0.012 µg/ml of paclitaxel results in the greatest synergy (a mutually exclusive CI value of 0.246). This is 60% lower than that of the 24-h exposure.

After the SCC-9 24-h exposure with a paclitaxel concentration of 0.012 µg/ml, there was no evidence of synergism at radiation doses of 0.1–3 Gy (mutually exclusive CI values of 1.497, 1.625, 1.679, and 1.691) or at a paclitaxel concentration of 0.006 µg/ml and 3 Gy of radiation (mutually exclusive CI value of 1.904). However, after a
48-h paclitaxel exposure, CI values decreased to less than 1 for all of these dose combinations. The mutually exclusive CI values were 0.522, 0.403, 0.366, and 0.291 for a paclitaxel concentration of 0.012 µg/ml and 0.1, 0.3, 1, and 3 Gy of radiation, respectively, and 0.771 for a paclitaxel concentration of 0.006 µg/ml and 3 Gy of radiation. On the other hand, the synergism that had originally been noted in the lower doses of both modalities is no longer present. At a paclitaxel concentration of 0.002 µg/ml combined with 0.1 Gy of radiation, the CI value is now above 1 (1.038). Mutually exclusive CI values also were noted to change from 0.770 to 1.689 and from 0.615 to 1.081 for combinations of 0.002 µg/ml of paclitaxel and 6 Gy of radiation, and 0.06 µg/ml of paclitaxel and 0.1 Gy of radiation, respectively.

Table 3 displays the mutually exclusive CI values of HEP-2 cells after a 48-h treatment of both increasing paclitaxel concentrations and increasing doses of radiation. Generally, the multiphasic pattern of synergism seen in the 24-h paclitaxel exposure of the SCC-9 cell line was similar for the 48-h paclitaxel exposure of the HEP-2 cell line. CI values slightly less than 1 result in the lowest dose ranges of each modality (indicating a weak synergy) and far less than 1 in the highest dose ranges (indicating the greatest synergy). Likewise, the lowest CI values (denoting the greatest synergism) are at a paclitaxel concentration of 0.012 µg/ml combined with 3 and 6 Gy of radiation (mutually exclusive CI values of 0.377 and 0.284, respectively). Although mutually exclusive CI values suggest a mild synergism for 0.006 µg/ml of paclitaxel and radiation doses of 1 and 3 Gy as well as 0.0006 µg/ml of paclitaxel with 3 Gy of radiation (0.910, 0.894, and 0.935, respectively), mutually nonexclusive values (1.00, 1.056, and 1.148, respectively) show that the interaction at these doses may be only additive.

**DISCUSSION**

In this study, we found synergistic interactions between paclitaxel and radiation against two squamous carcinoma cell lines of head and neck origin, indicating a radiosensitization by paclitaxel. This synergistic interaction occurred at concentrations of paclitaxel and radiation doses that are used clinically. The data indicate that daily radiation fractions with daily or once weekly doses of paclitaxel should provide synergistic interactions in head and neck cancer patients.

Paclitaxel alone in concentrations of 0.01 µg/ml or higher produced...
a marked accumulation of cells from both cell lines in the G2-M phases of the cell cycle. In addition, there was an increase in the sub-G1 population, which represents an increase in an apoptotic population. Although the G2-M arrest itself may lead to subsequent apoptosis, it may not be required for the apoptotic death of these sub-G1 cells. Other reports have noted that paclitaxel may exert a second mechanism of toxicity at a phase of the cell cycle other than the well-established G2-M arrest (10). Wahl et al. (28) demonstrated that loss of p53 expression had an integral and multiphasic role in paclitaxel-induced cytotoxicity. At low paclitaxel concentrations, cells with intact p53 function had a relative resistance to a G2-M arrest that was overcome at higher concentrations. The same paclitaxel concentrations noted above (0.01 μg/ml or higher) were also cytotoxic to the squamous carcinoma cell lines that we studied. Radiation doses above 1 Gy were required for 50% cell kill of the cell lines examined, and 10 Gy or more were required for greater than 1 log cell kill. When the radiation fractions were delivered after exposure to various concentrations of paclitaxel, enhanced cytotoxicity was noted in a multiphasic, dose- and time-dependent manner.

True radiosensitization can be defined as a synergistic or additive interaction between paclitaxel and radiation. To determine whether the paclitaxel-radiation interaction was synergistic, we used the CI analysis described by Chou et al. (21–26). Through this isobologram type analysis, we found a multiphasic synergy in 24- and 48-h paclitaxel exposures before radiation. At high radiation doses (10 Gy), synergism was noted at all paclitaxel concentrations. Similarly, at high paclitaxel concentrations (0.06 μg/ml and above) synergism was noted with all radiation doses down to 0.1 Gy. With low to moderate radiation doses (0.1–3 Gy) and low paclitaxel concentrations (0.002–0.006 μg/ml), the synergistic interaction was generally absent. Interestingly, the lowest paclitaxel concentrations (0.0006 μg/ml for HEP-2 and 0.002 μg/ml for SCC-9) and the lowest radiation doses produced synergistic interactions not observed at slightly higher concentrations. In SCC-9 cells, prolonged exposure (48 h) lowered the radiation dose required to give synergistic interactions.

The paclitaxel concentrations and radiation doses used in these studies were within those achieved clinically in patients. Short paclitaxel infusions (1–3 h) of 175–250 mg/m² result in peak plasma concentrations as high as 10 μg/ml, with levels exceeding 0.006 μg/ml for as long as 6–9 days (29, 30). These doses are generally given at 3-week intervals. At weekly intervals with radiation therapy, paclitaxel doses of 45–60 mg/m² are generally used. These produce plasma levels exceeding 0.006 μg/ml for 3–4 days, during which, radiation doses of 1.8–2 Gy are usually delivered. Thus, maximum synergy should be observed clinically with weekly paclitaxel and daily radiation.

Other than the present study, only four studies evaluating the interactions of paclitaxel and radiation addressed the issue of synergy in a quantitative manner. Three of these concluded that the interaction was supraadditive or synergistic, using leukemia cells (11), squamous carcinoma cells (13, 20), adenocarcinoma cells (18, 19), and fibroblasts (20). As in our study, Hennequin et al. (20) noted that the paclitaxel-radiation interaction was synergistic and multiphasic with low paclitaxel or docetaxel doses resulting in additive effects, moderate doses in antagonistic effects, and higher doses in synergistic effects. In these studies, the accumulation of cells in G2-M was often used to explain the synergistic interactions. In an in vivo study, Milas et al. (19) also proposed that reoxygenation could play a role. However, it is unlikely that reoxygenation played a role in our in vitro studies. Although the G2-M accumulation produced by paclitaxel at moderate and higher
concentrations may have been responsible for the synergistic interactions in our study at these concentration, it cannot explain the paradoxical synergism at very low paclitaxel concentration/radiation doses (e.g., 0.0006 μg/ml and 0.1 Gy for the HEP-2 cell line after a 48-h paclitaxel exposure). The multiphasic synergism observed may be explained by more than one mechanism in which paclitaxel concentration, exposure time, p53 expression, G2-M accumulation, and non-G2-M-dependent apoptotic effects determine which one of competing mechanisms exerts a dominant effect.

The reason that no interaction was found among 9 of 26 cell lines studied is not entirely clear. Contradictory results were sometimes observed in the same adenocarcinoma cell lines (i.e., MCF-7 and DU145) and among cervical squamous carcinoma cell lines (four showed sensitivity whereas another four did not). Some of the differences may have been due to the concentration and duration of paclitaxel exposure as illustrated in Table 4. For example, the two studies with conflicting conclusions of the radiosensitizing properties of paclitaxel in the same cell line assayed different concentrations of paclitaxel (see Table 4). The highest paclitaxel concentration used in the study by Stromberg et al. (15) study of the MCF-7 cell line was 0.0085 μg/ml, whereas Liebman et al. (12) used higher concentrations of paclitaxel. Liebman et al. (12) also showed that the degree of sensitization was time dependent after analyzing 48- and 72-h exposure periods in addition to the 12- and 24-h periods of Stromberg et al. (15). The paclitaxel concentrations of Lokeshwar et al. (14) and Stromberg et al. (15) were comparable, although the highest paclitaxel concentration used by Lokeshwar et al. was 0.0425 μg/ml. This was slightly over one-third higher than the highest concentration of Stromberg et al. (0.031875 μg/ml). The low paclitaxel concentrations and the short exposure durations may have accounted for the negative effect.

Table 4 Times of paclitaxel exposure and paclitaxel concentrations in three studies that showed contradictory results in the same cell lines

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Cell line</th>
<th>Time of paclitaxel exposure (h)</th>
<th>Paclitaxel concentration (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liebman (12)</td>
<td>MCF-7</td>
<td>12, 24, 48, and 72</td>
<td>0.0085, 0.085, 0.85, and 8.5</td>
</tr>
<tr>
<td>Stromberg (15)</td>
<td>MCF-7</td>
<td>12 and 24 h</td>
<td>0.0017, 0.00425, and 0.0085</td>
</tr>
<tr>
<td>Stromberg (15)</td>
<td>DU145</td>
<td>12 and 24</td>
<td>0.0085, 0.01275, and 0.031875</td>
</tr>
<tr>
<td>Lokeshwar (14)</td>
<td>DU145</td>
<td>4, 8, 14, 18, and 24</td>
<td>0.00085, 0.0085, and 0.0425</td>
</tr>
</tbody>
</table>

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REFERENCES


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