In Vitro Concurrent Paclitaxel and Radiation of Four Vulvar Squamous Cell Carcinoma Cell Lines

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BACKGROUND. The antitubule agent paclitaxel causes a cell cycle blockage in the most radiosensitive part of the cell cycle, the G_2/M phase. The possible radiosensitizing effect of paclitaxel was tested in four vulvar (UM-SCV-1A, UM-SCV-1B, UM-SCV-2, and UM-SCV-4) squamous cell carcinoma (SCC) cell lines.

METHODS. A 96-well plate clonogenic assay was performed with paclitaxel and radiation, both separately and concomitantly. Survival data were fitted to the linear quadratic model. The area under the curve, equivalent to the mean inactivation dose (D), was obtained by numerical integration. The effect of paclitaxel on radiosensitivity was measured as the AUC ratio (paclitaxel plus radiation: radiation alone). This ratio was compared with the surviving fraction (SF_P) after paclitaxel alone.

RESULTS. Paclitaxel concentrations of 0.4 to 2.0 nanomolar (nM) caused 1 to 70% inhibition of clonogenic survival. The AUC values of the cell lines were 1.9 to 2.9 gray. A full additive effect was observed when paclitaxel and radiation were administered concurrently; however, a supra-additive effect never occurred. The type of paclitaxel radiation interaction was not affected by the concentration of the drug nor did the type of interaction vary between cell lines studied.

CONCLUSIONS. Paclitaxel and radiation used concomitantly produced a clear additive effect at all concentrations and in all vulvar carcinoma cell lines tested. Although no supra-additive effect was observed, the additive effect already in nM concentrations could be beneficial in clinical use and, therefore, requires further investigation. ***Cancer* 1996; 77:1940–6.** © *1996 American Cancer Society.*

KEYWORDS: paclitaxel, radiosensitizer, vulvar carcinoma, squamous cell carcinoma, clonogenic assay.

Paclitaxel (Taxol® Bristol-Myers, Squibb Company, Princeton, NJ) is a new chemotherapeutic agent, derived from the bark of the Pacific yew (Taxus brevifolia).[1] It has known antitumor activity in many tumor types[2] and has mostly been used in the treatment of breast, ovarian, and non-small cell lung cancer.[3–5] Paclitaxel acts as a microtubular inhibitor by enhancing the rate and yield of microtubular assembly and by preventing microtubular depolymerization. This results in accumulation of the cells in the G2/M phase of the cell cycle,[6] the most sensitive to irradiation. This type of modulation of the cell cycle encourages physicians to utilize paclitaxel concomitantly with radiation to produce radiosensitization of the tumor cells. If doses of both treatment modalities can be reduced due to simultaneous administration, and normal tissue reactions are not enhanced, side effects could be minimized. Furthermore, sterilization of micrometastasis is needed to inhibit dissemination of locally advanced disease.

Surgery has been the cornerstone of vulvar cancer treatment. As an alternative to extensive surgery, chemoradiation has become the primary treatment modality to an increasing extent for advanced stage vulvar

TABLE 1
Characteristics of the Cell Lines

Cell line	Origin	Clinical stage[a]	Histology[b]	Specimen site	Prior therapy	Reference
UM-SCV-1A	Vulva	T3N3M1	Well-poor	Primary	None	10
UM-SCV-1B	Vulva	T3N3M1	Poor	Pleural effusion	None	10
UM-SCV-2	Vulva	T3N1M0	Poor	Local recurrence	Surgery	11
UM-SCV-4	Vulva	T2N2M0	SCC	Primary	None	11

[a] TNM status of primary tumors according to American Joint Committee of Staging.
[b] Histologic grading: well, moderately, or poorly differentiated squamous cell carcinoma.

TABLE 2
Cell Lines, Passages Used, Plating Efficiency, Intrinsic Radiosensitivity, α and β Parameters of the Linear Quadratic Model, Surviving Fraction at 2 Gray and Sensitivity to Paclitaxel

Cell lines	Passages used	Plating efficiency	Intrinsic radiosensitivity[a] (AUC)(Gy)	α (1/Gy)	β (1/Gy^2)	SF2	Sensitivity to paclitaxel (IC_{50}) nM
UM-SCV-1A	27–37	0.50–0.67	2.2 ± 0.1	0.43	0.0050	0.41 ± 0.02	1.7 ± 0.3
UM-SCV-1B	25–30	0.48–0.56	2.9 ± 0.1	0.31	0.0053	0.53 ± 0.03	1.7 ± 0.1
UM-SCV-2	28–35	0.52–0.78	2.3 ± 0.2	0.27	0.010	0.56 ± 0.06	0.81 ± 0.12
UM-SCV-4	17–25	0.20–0.82	1.9 ± 0.1	0.53	0.000019	0.35 ± 0.04	0.6 ± 0.1

AUC: area under the surviving curve; SF: survival fraction; Gy: gray; nm: nanomolar.
[a] AUC equivalent to mean inactivation dose.

TABLE 3
Effects of Paclitaxel on Clonogenic Survival of Four Vulvar Squamous Cell Carcinoma Lines Used as a Single Agent and Concomitantly with Radiation

Cell lines	Paclitaxel dose (nM)	SF_D ± SD[a]	(AUC_{P+R}/AUC_R) ± SD[b]	α[c] (1/Gy)
UM-SCV-1A	0.8	0.88 ± 0.02	0.88 ± 0.02	0.35
	1	0.80 ± 0.13	0.81 ± 0.13	0.41
	1.5	0.47 ± 0.06	0.55 ± 0.22	0.31
UM-SCV-1B	1.2	0.77 ± 0.05	0.81 ± 0.05	0.30
	1.5	0.70 ± 0.08	0.73 ± 0.04	0.33
	2	0.30 ± 0.03	0.33 ± 0.03	0.14
UM-SCV-2	0.5	0.83 ± 0.05	0.90 ± 0.04	0.20
	0.6	0.85 ± 0.10	0.74 ± 0.08	0.36
	0.8	0.56 ± 0.19	0.52 ± 0.12	0.32
UM-SCV-4	0.4	1 ± 0.1	0.95 ± 0.08	0.53
	0.5	0.87 ± 0.10	0.84 ± 0.06	0.50
	0.7	0.58 ± 0.08	0.46 ± 0.08	0.65

nM: nanomolar; SF: surviving fraction; SD: standard deviation; AUC: area under the survival curve; Gy: gray.
[a] Surviving fraction obtained using indicated doses of paclitaxel as a single agent.
[b] The ratio between the AUC of cultures incubated with different doses of paclitaxel concomitantly with radiation, divided by the AUC after radiation alone.
[c] α-parameter for the survival curve of the concomitant use of paclitaxel and radiation.

cancer[7–11] in this decade. In most of the chemoradiation studies, the drugs used concurrently with radiation are cisplatin and 5-fluorouracil (5-FU). Survival for patients treated with chemoradiation appears to be as long as or longer than that for patients treated with primary radical surgery.[7,8]

The majority of vulvar cancer is of squamous cell origin. We have recently established and characterized a panel of human vulvar squamous cell carcinoma (SCC) lines.[12,13] We have also developed a method suitable for exploring the cytotoxic effects of irradiation and chemotherapeutic agents, and their concomitant use in vitro.[14,15]

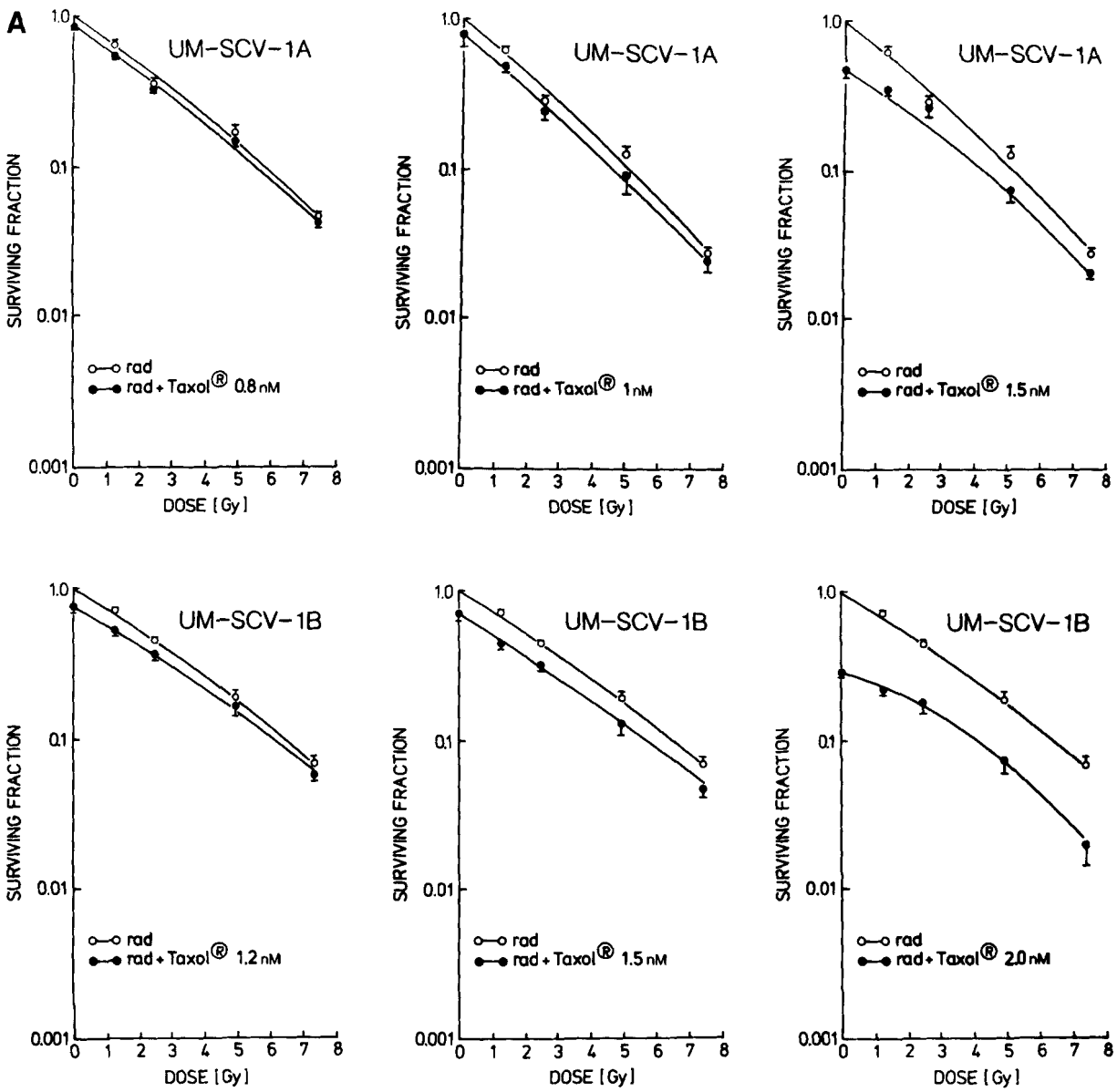

FIGURE 1. The effect of simultaneously used paclitaxel and acute radiation on the vulvar cell lines UM-SCV-1A and UM-SCV-1B (A), and UM-SCV-2 and UM-SCV-4 (B). The figures show fitted radiation survival curves for each cell line without paclitaxel (Taxol®) (○) and combined with the indicated paclitaxel dose (●). The results are given as the average of the actual data points and the bars represent one standard deviation.

The intrinsic radiosensitivity of these vulvar SCC lines varies, but most of them are clearly more radioresistant than cervical SCC and endometrial adenocarcinoma lines tested with the same assay.[16–18] Since advanced vulvar cancer presents a difficult therapeutic challenge, it was in our interest to test the in vitro effect of simultaneous paclitaxel and irradiation. This study focuses on paclitaxel as a potential radiosensitizing agent in SCC of the vulva. Supra-additivity in in vitro experiments would indicate a true radiosensitizing effect.

MATERIALS AND METHODS

Cell Lines and Cell Culture

We have tested the sensitivity of 8 vulvar carcinoma cell lines to paclitaxel (unpublished data). For this experiment, we chose 4 cell lines with dissimilar paclitaxel sensitivity. Three of the cell lines (UM-SCV-1A, UM-SCV-2, and UM-SCV-4) have been established from primary tumors, and the UM-SCV-1B line from a pleural effusion. UM-SCV-1A and UM-SCV-1B were derived from the same patient at primary diagnosis. Characteristics of the cell

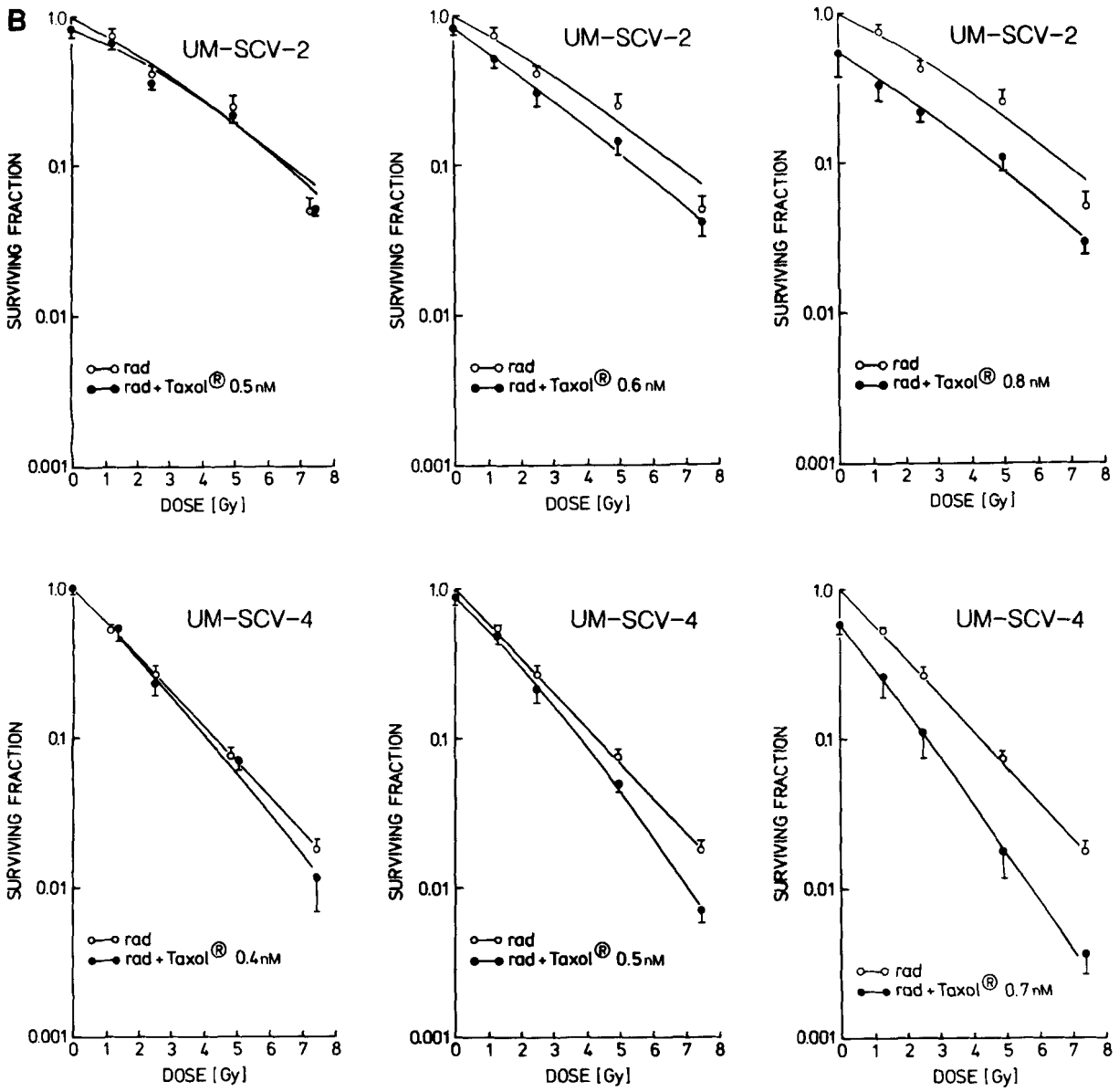

FIGURE 1. *(continued)*

lines are listed in Table 1. Prior to the experiments, cells were grown in Dulbecco's modified Eagle's minimal essential medium containing 2 mM glutamine, 1% nonessential amino acids, 100 U/mL penicillin, 100 U/mL streptomycin, and 10% fetal bovine serum (FBS). The cells were kept in logarithmic growth by passing them weekly or biweekly.

Drug Preparation

Paclitaxel (Bristol–Myers Squibb, Princeton, NJ) was received as an infusion concentrate of 6 mg/mL. Stock solution of 100 nM was prepared in Ham's F-12 medium, kept at −18 °C, and thawed immediately before the experiments. Based on the knowledge from the previous experiments, we chose three paclitaxel concentrations causing 1–70% inhibition of clonogenic survival for each cell line. Final dilutions of 0.4–2 nM paclitaxel were used for experiments.

Clonogenic Assay and Irradiation

The cells were grown in T25 culture flasks to midlogarithmic phase (40–60% confluency) and fed with fresh medium on the day before plating for the experiments. The clonogenic assay was performed as described previously.[19] Shortly, the

cells were harvested with trypsin and ethylenediamine-tetraacetic acid (EDTA), counted, and diluted to a stock solution of 4167 cells/mL. The number of cells plated per well was adjusted according to the plating efficiency of each cell line. Further dilutions of this single cell solution either with or without paclitaxel were made in 50 mL of Ham's F-12 medium containing 15% FBS. The cells were plated in 96-well culture plates by applying 200 μL per well using an octapipette. Two to 3 experiments including duplicate plates were carried out on each cell line to test the effect of radiation alone, paclitaxel alone, and the combination of these two. The same single cell solution was always used as the source of cells in one experiment. After plating into the 96-well plates, the cells were allowed to attach for 24 hours prior to irradiation. To test the concomitant use of paclitaxel and radiation, the cells were treated with paclitaxel for 24 hours before irradiation, and the drug was allowed to remain in the plates during the whole incubation period.

The cells were irradiated in plates with 4 MeV photons generated by a linear accelerator (Clinac 4/100, Varian, Palo Alto, CA) which delivers a dose-rate of 2 grays (Gy) per minute. The radiation doses used were 1.25, 2.5, 5, and 7.5 Gy. Detailed dosimetry has been published previously.[20] The plates were incubated in a water vapor-saturated atmosphere containing 5% CO_2 at 37 °C. After four weeks, the number of positive wells was counted using an inverted phase-contrast microscope. Wells with colonies consisting of at least 32 cells were considered positive.

Data Analysis

Plating efficiency was calculated using the formula -1n(number of negative wells/total number of wells) per number of cells plated per well. Fraction survival data as a function of the radiation dose with or without indicated paclitaxel dose was found to be fitted in the linear quadratic equation. A microcomputer program was used to fit data to $F = A * \exp[-(\alpha D + \beta D^2)]$. Area under the curve (AUC) value, equivalent to mean inactivation dose (D), was obtained by numerical integration. AUC-ratio (AUC for paclitaxel + radiation/AUC for radiation) and surviving fraction after the indicated dose of paclitaxel (SF_P) were used to compare the effect of combined paclitaxel and irradiation with the effects of paclitaxel alone.

RESULTS

Four vulvar SCC cell lines were evaluated in this study. The plating efficiencies, passages used, information about the intrinsic radiosensitivity expressed as mean inactivation dose (AUC), surviving fraction at 2 Gy (SF2), and sensitivity to paclitaxel are summarized in Table 2.

The achieved differences in survival when paclitaxel and radiation were used concomitantly are given in Table 3. A clear additive growth inhibitory effect was seen during the simultaneous use of paclitaxel and radiation (Fig. 1). However, no supra-additivity was noticed since the effect of simultaneous paclitaxel and radiation was of the same magnitude as that calculated by combining the cytotoxic effects of the two modalities alone. The differences in chemosensitivity between cell lines did not affect the paclitaxel-radiation synergy. Nor did the increasing dose of paclitaxel modulate the type of interaction. The survival curves comparing radiation alone and concomitant drug and radiation are clearly parallel in 3 out of 4 cell lines. The survival curves of UM-SCV-4, obtained in experiments with combined paclitaxel and radiation, tend to be steeper than the survival curve of radiation alone, but still the standard errors of the AUC-ratios and SF_Ps are overlapping. α-parameters for survival curves of concomitant treatment do not consistently become higher compared with irradiation only. Thus, studied with this parameter, our results do not indicate a supra-additive effect during simultaneous administration of paclitaxel and radiation.

DISCUSSION

The poor prognosis of advanced vulvar carcinoma indicates a need for the development of multimodality therapies including surgery, radiotherapy, or chemotherapy. For this task, the knowledge of the radiobiologic characteristics of vulvar carcinoma and its sensitivity to different chemotherapeutic agents is essential. In vitro techniques like clonogenic assays provide the best means for elucidating these properties in preclinical studies. In this study, we evaluated the possible radiosensitizing effect of Taxol on four vulvar SCC lines in vitro. Our results exhibited a strictly additive growth inhibitory effect when the cells were exposed to radiation and paclitaxel simultaneously.

Concurrent use of radiation and chemotherapeutic agents for the treatment of gynecologic malignancies has been an interest of several investigators over the last few years. In clinical trials, the use of 5-FU or cisplatin in combination with radiation has been shown to be a feasible approach to better local tumor control in the management of vulvar and cervical carcinoma.[7,8,21,22] This type of chemoradiation therapy is an effective new alternative for treatment of advanced vulvar cancer and could eventually replace radical surgery as the primary treatment for these advanced cases.[7-11] Accordingly, in recurrent cases after initial chemoradiation therapy, less radical surgery could be sufficient.

During concurrent use of paclitaxel and radiation a supra-additive effect can be expected due to the ability of paclitaxel to synchronize cells in the radiosensitive phases of the cell cycle. Melanoma, breast and ovarian adenocarcinoma, leukemia, and prostatic carcinoma cell lines have been reported to show enhancement of radia-

tion sensitivity during concomitant use of paclitaxel and radiation.[23-27] Tishler et al have reported a radiosensitizing effect from paclitaxel in a dose dependent manner in a human astrosytoma cell line. They have also demonstrated that the cells exposed to paclitaxel accumulate in the G2/M phases of the cell cycle. It has been suggested that radiosensitization by paclitaxel requires the production of a G2/M cell cycle block.[24] However, Steren et al noticed radiosensitization in ovarian cancer cells with paclitaxel at subtherapeutic doses and even at concentrations that did not cause any cytotoxicity or cell cycle perturbations.[25] In our previous work, clearly subclinical doses caused complete inhibition of clonogenic growth (unpublished data). Therefore, we used doses below the achievable peak plasma concentration in the current study. In our chemoradiation experiments, the utmost concentrations of paclitaxel causing 1% (UMSCV-4) or 70% (UM-SCV-1B) growth inhibition did not show any dose-dependent change in the type of synergy. Results were consistent in all cell lines exhibiting a full additive effect.

Paclitaxel appears to act as a radiosensitizer only in some human tumor cell lines. A clearly additive effect in concomitant use of paclitaxel has been shown in lung adenocarcinoma and two cervical carcinoma cell lines.[29,30] These investigators have suggested that cell lines with small intrinsic α component or relative radioresistance would be expected to be most sensitized by paclitaxel. Our results do not support that hypothesis. Vulvar SCC lines are relatively radioresistant as a group and show no supra-additivity during combined exposure to paclitaxel and radiation. Furthermore, the intrinsic radiosensitivity of the cell lines did not modulate the type of interaction.

A supra-additive effect has been seen only with higher doses of radiation in mouse embryo fibroblasts showing otherwise additive interaction of paclitaxel and irradiation.[31] An increase in the extent of radiopotentiation by paclitaxel with increasing irradiation dose has also been reported in mouse mammary carcinoma.[32] Vulvar SCC lines do not present any paclitaxel induced enhancement in radiation sensitivity within standard error. However, there was a tendency of the survival curve for UM-SCV-4 cell line with paclitaxel exposure to get steeper with increasing radiation doses. This could indicate a need for greater radiation doses to produce a radiosensitizing effect. Further conclusions of this type of modulation cannot be made because of the limited material.

Our results on concurrent use of paclitaxel and radiation in vulvar SCC in vitro show an additive cytotoxic effect and are encouraging. Although radiosensitizing would be a desirable property of a chemotherapeutic agent, it is not crucial for successful chemoradiation therapy. Clear additivity is also favorable when it leads to better local control of the tumor and allows a reduction in both radiation and drug doses without compromising treatment results. The optimum dosage and administration schedule of the drug with respect to irradiation are not yet settled. The effect of paclitaxel as a radiosensitizer in combination with fractionated radiotherapy would be of interest to study in the future as well as a comparison with other chemotherapeutic drugs, e.g., cisplatin and 5-FU, used currently in chemoradiation in the treatment of vulvar carcinoma. Clinical trials are needed for further evaluation of the concurrent use of paclitaxel and radiation in the treatment of vulvar cancer.

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