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# LETTER TO THE EDITOR

*Dear Sir,*

**Non-immunosuppressive cyclosporine derivative PSC 833 abolishes resistance of human multidrug-resistant ovarian carcinoma cells *in vitro* to paclitaxel and paclitaxel-induced radiosensitization**

*Paclitaxel has been shown to enhance the cytotoxic effects of ionizing radiation on human leukemia (Choy* et al., *1993), ovarian carcinoma (Steren* et al., *1993; Choy* et al., *1994), astrocytoma (Tishler* et al., *1992) and head and neck carcinoma (Leonard* et al., *1996) cells* in vitro. *Data on concurrent or subsequent use of paclitaxel and radiotherapy in the treatment of head and neck (Rosenthal and Carbone, 1995), breast (O'Shaugnessy and Cowan, 1994) and lung (Choy* et al., *1994) carcinoma patients have been reported. Paclitaxel also stimulates the cytotoxic effect of ionizing radiation in human multidrug-resistant leukemia cells* in vitro *(Mote* et al., *1996). Our previous data (Sedlak* et al., *1997) have shown that human multidrug-resistant (MDR-1) leukemia cells* in vitro *are relatively resistant to paclitaxel and to sequential exposure to paclitaxel and ionizing radiation at concentrations of paclitaxel higher by at least one order of magnitude than those efficient in parental drug-sensitive cells.*

*The non-immunosuppressive cyclosporine derivative SDZ PSC 833 has been shown to reverse multidrug-resistance of neoplastic cells, including the* MDR-1 *gene-coded P-glycoprotein (Pgp)-mediated cells resistant to paclitaxel (Jachez* et al., *1993), and thus to be one of most efficient drug-resistance modulators (Gavériaux* et al., *1991; Thiberghien and Loor, 1996).*

*We examined the abrogation of resistance to paclitaxel-induced sensitization to ionizing radiation in the multidrug-resistant ovarian carcinoma cells A2780/ADR (obtained from Dr. A. McGown, Manchester, UK). This cell line has been shown previously to over-express P-gp and to exhibit verapamil-sensitive decreased drug (daunomycin) accumulation (Sedlak* et al., *1996). These multidrug-resistant cells were exposed for a short (1 hr) period to paclitaxel (Sigma, St. Louis, MO) with or without SDZ PSC 833 (Sandoz, Basle, Switzerland), with a subsequent 24-hr incubation in paclitaxel-free medium, irradiation (Siemens Stabilipan, Karlsruhe, Germany) at doses of 2 or 4 Gy and evaluation of viability using a photometric MTT test 96 hr after irradiation. Measurements at each paclitaxel concentration were performed at least in triplicate and repeated 4 times with a statistical evaluation using a 2-tailed* t-test.

*A2780/ADR cells were resistant to paclitaxel (Fig. 1); to paclitaxel-induced cell cycle alterations,* i.e., *the accumulation of paclitaxel-treated cells in the $G_2$/M phase of the cell cycle (Table I); and to paclitaxel-induced radiosensitization. The $SF_2/SF_0$ ratios (the ratio of median of survival fraction after 2 Gy to median of survival fraction of unirradiated cells) for all examined paclitaxel concentrations were 0.61 ± 0.195 in parental A2780 cells and 0.99 ± 0.070 in drug-resistant A2780/ADR cells ($p < 0.0018$). The non-immunosuppressive cyclosporine derivative SDZ PSC 833 abolished the resistance of A2780/ADR cells to paclitaxel (Fig. 1), to paclitaxel-induced cell cycle alterations (Table I) and partially to the resistance to the radiosensitizing effect of paclitaxel pre-treatment (the $SF_2/SF_0$ ratio was 0.99 ± 0.070 in A2780/ADR cells and 0.79 ± 009 in the same cells treated with SDZ PSC 833;* $p < 0.0004$).

*Our results confirm the findings of Griffon-Etienne* et al. *(1996), showing a radiosensitizing effect of paclitaxel on A2780 cells, adding data on paclitaxel-induced radiosensitization of drug-resistant A2780/ADR cells treated with the non-immunosuppressive cyclosporine derivative SDZ PSC 833.*

*The therapeutic potential of paclitaxel as a radiosensitizer is being studied clinically. It can be expected that SDZ PSC 833 or a resistance-modifying agent with similar properties may contribute to the efficacy of chemoradiotherapy utilizing the potential of taxanes to act as radiosensitizers. Since SDZ PSC 833 decreases the biotolerability and increases the neurotoxicity of toxic substances, possibly by inhibiting Pgp function at the blood–brain barrier (Didier and Loor, 1995), it is indeed a type of resistance modifier that might be studied for its ability to sensitize brain tumor cells to anti-cancer drugs and for its radiosensitizing potential.*

*Sincerely yours,*

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**TABLE I** – ALTERATIONS OF CELL CYCLE INDUCED WITH PACLITAXEL ALONE AND IN COMBINATION WITH SDZ PSC 833 IN PARENTAL A2780 AND MULTIDRUG-RESISTANT A2780/ADR CELLS *IN VITRO*

| | % in cell cycle phase | | | | | |
|---|---|---|---|---|---|---|
| | A2780 | | | A2780/ADR | | |
| | $G_0/G_1$ | S | $G_2/M$ | $G_0/G_1$ | S | $G_2/M$ |
| None | 61.3 ± 4.06 | 18.6 ± 4.33 | 20.1 ± 1.95 | 59.8 ± 4.44 | 29.3 ± 4.60 | 11.0 ± 3.54 |
| Paclitaxel (0.1 µM) | 5.0 ± 1.87 | 33.5 ± 8.65 | 61.5 ± 7.76 | 59.5 ± 3.20 | 26.3 ± 1.92 | 14.3 ± 2.05 |
| SDZ PSC 833 (5 µM) | 63.5 ± 4.03 | 17.5 ± 6.50 | 19.0 ± 2.92 | 58.5 ± 4.77 | 27.8 ± 5.31 | 13.8 ± 2.86 |
| Paclitaxel, PSC 833 | 5.5 ± 2.06 | 29.3 ± 6.22 | 65.3 ± 6.38 | 11.0 ± 2.74 | 12.5 ± 2.60 | 76.5 ± 5.12 |

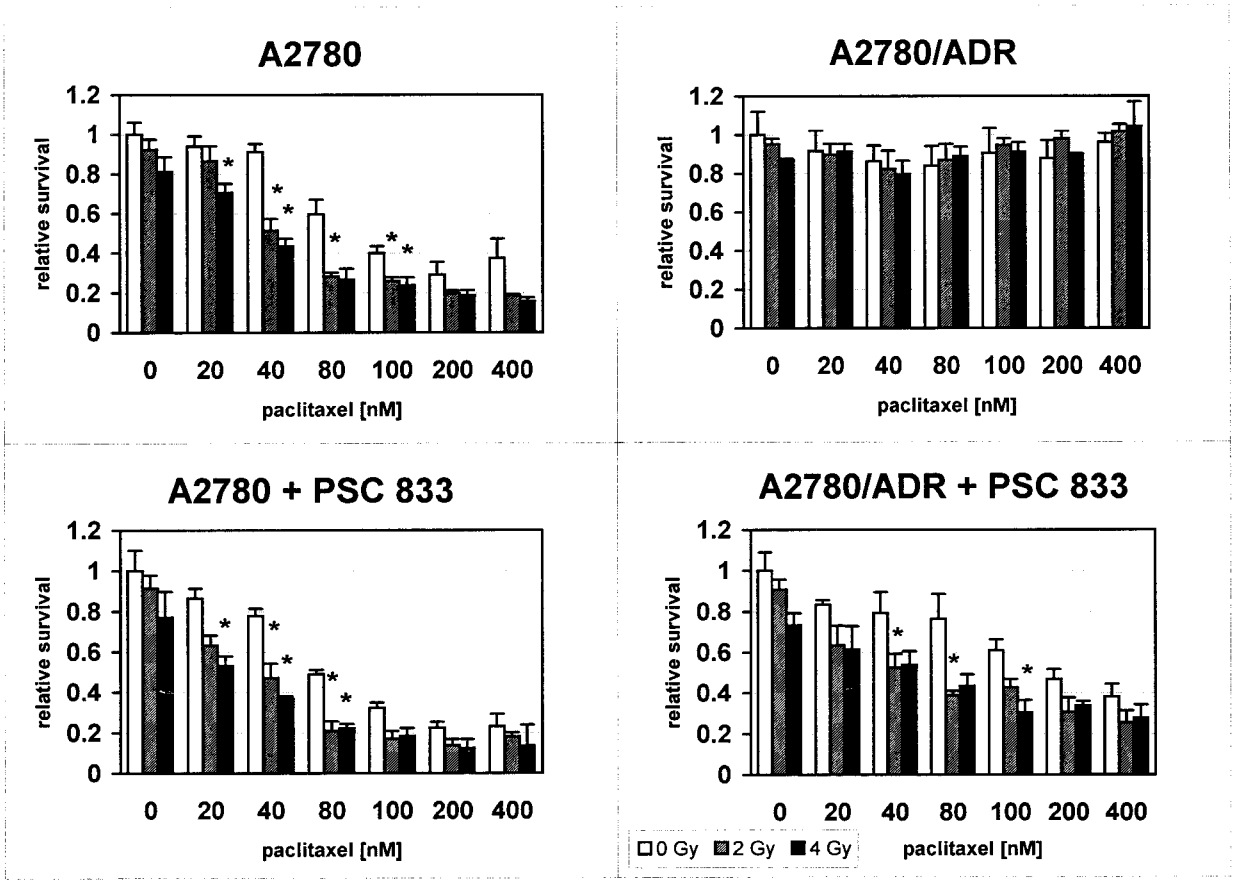


**FIGURE 1** – Survival of A2780 and A2780/ADR cells treated with different concentrations of paclitaxel and ionizing radiation in the presence of the cyclosporine analog SDZ PSC 833. Columns correspond to the mean values from 4 experiments ± SD; asterisks indicate statistically significant ($p < 0.05$) differences between survival of unirradiated and irradiated cells at indicated paclitaxel concentrations.

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