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## Radiosensitizing effect and pharmacokinetics of Doranidazole in suit-2 human pancreatic cancer xenografted in mouse pancreas

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Propose: To investigate the efficacy and pharmacokinetics of a hypoxic cell sensitizer Doranidazole (PR-350) in human pancreatic cancer cells in vitro and in vivo.

**Methods:** Suit-2 human pancreatic cancer cells were used.

In vitro, radiosensitizind effect of Doranidazole was investigated under aerobic and hypoxic conditions. In vivo, the tumor cells were implanted in the pancreas of Balb/c nude mice, and effect of single dose irradiation with or without Doranidazole was assessed by measuring tumor weight 5 days later. Concentrations of Doranidazole in the seram and panceatic tumor were measured by high-performance liquid chromatography.

**Results:** The in vitro sensitizer enhancement ratio was 1.25 at 0.4 mM and 1.5 at 1 mM. Doranidazole had in vivo radiosensitizing effect when 100, 150 or 200 mg/kg of the durg was combined with single 5 Gy irradiation. The tumor/serum concetration ratio was 0.3–0.4, and the peak concentration in the tumor was 141 micro-g/g at the dose of 200 mg/kg.

**Conclusion:** Doranidazole had radiosensitizing effest against suit-2 tumor cells in vitro. Also, it had in vivo effect even when combined with a relatively low radiation dose of 5 Gy. At doses of 100 mg/kg or higher, concentrations of Doranidazole in the pancreatic tumor appeared to be sufficient to obtain definite radiosensitization.

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## Interferon alfa 2b effect as chemosensitiser in a multidrug-resistant cell line

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**Purpose:** Multidrug resistance, a common problem in cancer treatment, is usually associated with the cellular overexpression of P-170-glycoprotein and Bcl-2 oncoprotein. The aims of our study were (1) to evaluate the effect of Interferon alfa 2b (Schering Plough) 500IU/ml, in combined treatment with doxorubicin 50 ng/ml, as a chemosensitiser in a colorectal carcinoma cell line (HCT-15), and (2) to evaluate if the combined treatment modifies the overexpression of the proteins P-170, Bcl-2 and Class I MHC in HCT-15 cells.

**Methods:** Chemosensibility was evaluated by inhibition of proliferation by incorporation of Tritiated Timidine and MTT assay. The expression of Proteins in the cell line was measured by flow cytometry.

**Results:** Doxorubicine cytotoxicity was potentiated by Interferon alfa 2b as observed by an inhibition of proliferation of 46.0 ± 1.1%, and of cell metabolism of 41.0 ± 4.2% ($p < 0.05$ and $p < 0.001$ respectively Vs. untreated controls).

Combined treatment also increased the expression of P-170 from 12.4 ± 2.5% to 24.8 ± 4.4% ($p < 0.05$), of Bcl-2 from 69.8 ± 2.3 to 93.4 ± 5.4% ($p < 0.01$) and of Class I MHC from 1.8 ± 1.4 to 12.3 ± 2.6% ($p < 0.01$) Vs. their untreated controls.

**Conclusion:** The sensibilization of the HCT-15 cells exerted by Interferon alfa 2b is not due to a decrease in P-170 expression. The augmented level of Bcl-2 would turn the effect of the drug to cytostatic, rather than cytotoxic. The elevated expression of Class I MHC obtained after treatment may improve the antigen presenting capacity of these cells to the inmune systems and suggests an efficient protocol for adjuvant chemotherapy.

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## Potential activity of Gemcitabine (GEM), Taxotere (TAX) and Navelbine (NAV) in anaplastic thyroid carcinoma

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Anaplastic thyroid carcinoma is one of the most aggressive and rapidly fatal human neoplasms. By combining surgery and external beam radiotherapy a better local control of disease has been achieved. Ultimately, distant metastases have gained importance as cause of death. So far, anaplastic thyroid carcinoma failed to adequately respond to any known chemotherapeutic approach. Consequently, identification of new active chemotherapeutic agents might improve qualitiy of life and survival. Thus, we investigated the in vitro activity of GEM, TAX, NAV, doxorubicin (DOX), cisplatin (CDDP), oxaliplatin (OX), and CPT-11 in the human anaplastic thyroid carcinoma cell lines SW1736 and 8505C. Cytotoxicity of a 1 h, 4 h and 24 h drug exposure was determined using the total protein sulforhodamine B assay and the results were summarized as $IC_{50}$ values ± SD (table, n = 3).

| Cell line | Drug | $IC_{50}$ (nM) | | |
|---|---|---|---|---|
| | | 1 h | 4 h | 24 h |
| SW1736 | GEM | 356.7 ± 11.55 | 202.5 ± 28.2 | 153.3 ± 15.3 |
| | TAX | 37.7 ± 9.29 | 11.3 ± 1.53 | 2.53 ± 0.84 |
| | NAV | 41.7 ± 2.88 | 28 ± 10.6 | 1.53 ± 0.12 |
| | DOX | 720 ± 216.3 | 156.7 ± 15.28 | 25 ± 0 |
| | CDDP | 43300 ± 11200 | 5200 ± 820 | 2200 ± 480 |
| | OX | >100000 | 14300 ± 5500 | 1100 ± 270 |
| | CPT-11 | >300000 | 15400 ± 4270 | 2600 ± 490 |
| 8505C | GEM | 1620 ± 277.5 | 158.3 ± 27.54 | 16.75 ± 2.75 |
| | TAX | 70.5 ± 1.29 | 20 ± 0 | 3.8 ± 2.0 |
| | NAV | 48.3 ± 19.3 | 27.3 ± 11.0 | 1.47 ± 0.46 |
| | DOX | 450 ± 140 | 130 ± 17.32 | 16.7 ± 4.04 |
| | CDDP | 31250 ± 9910 | 8180 ± 1380 | 1330 ± 210 |
| | OX | >100000 | 38300 ± 8080 | 4200 ± 1880 |
| | CPT-11 | >300000 | 15000 ± 2500 | 1940 ± 330 |

As determined by Relative Antitumor Activity (RAA = peak plasma concentration/$IC_{50}$-value), CPT-11, OX and CDDP appear to have only marginal activity, DOX moderate and GEM, TAX and NAV possibly high activity. In conclusion, as estimated by RAA CDDP has marginal and DOX moderate activity in anaplastic thyroid carcinoma which is in agreement with the clinical situation. Activity of CPT-11 and OX is weak whereas GEM, TAX and NAV exert potentially high activity. Further evaluation of TAX, GEM and NAV in anaplastic thyroid carcinoma seems promising.

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## Antitumour effect of chlorpromazine and dacarbazine on clear cell sarcoma xenografts

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**Aim:** Clear cell sarcoma has melanocytic features and is associated with tendons and aponeuroses. In the Scandinavian sarcoma registry only 18 cases (0.8%) of clear cell sarcoma were registered between 1986 and 1996. Four clear cell sarcoma cell lines obtained from patients have been reported in the literature.

Extensive surgery is the primary treatment.

The aim of the present study was to study the influence of temperature and effect on tumour growth of chlorpromazine when given in combination with dacarbazine, a drug used in the treatment of malignant melanoma.

**Method:** Human clear cell sarcoma tumour tissue was obtained during surgery of a 58-year old woman. The tumour (UMCCS-I) was maintained by serial s.c. transplantation's to the flank in nude mice.. Treatment with ip. injections were given to 4 groups (n = 8 in each group): (1) Dacarbazine (DTIC, 300 mg/kg), (2) chlorpromazine (15 mg/kg), (3) combination of DTIC and chlorpromazine or (4) saline (controls). In group 3 DTIC was given one hour after chlorpromazine. The animals treated with chlorpromazine were kept at an ambient temperature of 28 degrees centigrade (group 2 and 3) for 24 hours and group 1 and 4 at 24 degrees centigrade. Rectal temperature was measured hourly initially and tumour volume calculated twice weekly.

**Results:** No morbidity was observed. Chlorpromazine alone produced hypothermia (28 degrees centigrade) within an hour. Normal body temperature was reached after 10 hours. DTIC gave a transient decrease in temperature (3 degrees). In the combination group (3) the initial chlorpromazine-induced hypothermia was followed by a rapid rise in temperature after administration of DTIC. A second temperature-dip occurred in this group.

A tendency towards delayed tumour growth was noticed in the group treated with DTIC. Chlorpromazine alone did not influence the tumour growth. DTIC and chlorpromazine given in combination resulted in a significant antitumour effect.

**Conclusion:** A combination of DTIC and chlorpromazine has an antitumour effect on clear cell sarcoma in this tumour model. The influence of the temperature changes remains unclear. The results of this study on clear cell sarcoma suggests further investigations.