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EARLY CLINICAL STUDIES OF INTRAPERITONEAL MATRIX METALLOPROTEINASE INHIBITOR BB94 IN PATIENTS WITH MALIGNANT ASCITES

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BB94 is the first matrix metalloproteinase inhibitor (MPI) to enter clinical trial. In experimental systems MPIs affect tumour growth, haematogenous spread and tumour induced angiogenesis.

Animal models using a human ovarian carcinoma xenograft have indicated that BB94 increases survival in mice with malignant ascites. (Cancer Research 93: 53:2087.)

In a phase I study, 23 patients (P) with malignant ascites were treated with intraperitoneal BB94. The drug was well tolerated with no acute toxicity. Plasma levels of BB94 were maintained for greater than 28 days at levels above the therapeutic range in pre-clinical models. In 16 P there was no reaccumulation of ascitic fluid requiring redrainage within 28 days.

40 P were treated in phase II. Conventional criteria are hard to apply to ascites, but preliminary results suggest that 10 (25%) P responded (including 8/24 ovarian P).

Clinical data on all 63 patients will be presented.

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ISOLATION OF COMPETENT OVARIAN CARCINOMA CELLS FROM FRESH TUMOR TISSUE BY A MAGNETIC SEPARATION SYSTEM (MACS)

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Flow cytometric analysis of living ovarian carcinoma cells from fresh tumor tissue is hampered by the heterogenity of cells in the tumor and its stroma. We have established a model system for isolation of competent ovarian carcinoma cells from fresh tumor tissue: Fresh ovarian carcinoma tissue was subjected to mechanical disintegration and mild enzymatic treatment (0.005% collagenase D) to obtain single calls with intact surface antigens. To overcome the lack of tumor-cell specific antibodies, we used "negative tumor cell separation": Non-malignant cells were labeled with monoclonal antibodies against cell surface antigens: CD3 (T-cells), CD14 (monocytes), CD15 (granulocytes), CD45R (T-/B-cells), and 5B5 (fibroblasts). Rat-anti-mouse IgG antibodies coupled to ferrit microbeads (Miltenyi, Bergisch-Gladbach, Germany) were then added. Cells reacting with the microbeads were magnetically retained in a column filled with steel wool matrix (MACS, Miltenyi). Unlabeled tumor cells were washed through the column and recovered in the effluent. This method enables fast and simple isolation of single, competent tumor cells from fresh ovarian carcinoma tissue, ascitic or pleuritic effusions. In a model system consisting of cultured ovarian carcinoma cells and human leukocytes, tumor cell purity was 93%, and 97% after a second separation (recovery 75% and 50%). These still unlabeled tumor cells can be analyzed by flow cytometry or confocal laser scan microscopy for the presence of various surface antigens including receptors for proteases or growth factors. Analysis of cellular constituents such as RNA, DNA, and cell metabolites is also possible. After detergent treatment or fixation, flow cytometric multiparameter analysis such as simultaneous labeling of intracellular and surface antigens, as well as nuclear DNA staining (ploidy, S-phase), is possible.

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A PHASE II STUDY OF ALTERNATING PACLITAXEL AND CARBOPLATIN IN PATIENTS WITH ADVANCED OVARIAN CANCER

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Five cycles of paclitaxel 175 mg/m^2 (3 hrs. IV infusion) day 1 and carboplatin AUC 7 mg/ml/min. day 21 (cycle time 49 days) were used as firstline treatment in 30 patients with advanced ovarian cancer.

The WHO graded toxicities per cycle associated with this regime were:—Paclitaxel: Myalgia 60% Arthralgia 40% Paraesthesiae 25% Nausea and Vomiting 21% (G1-12%, G2-8%, G3-1%) Neutropaenia 81% (G1-12%, G2-22%, G3-32%, G4-15%) Thrombocytopaenia 2% (G2-1%, G3-1%). G3 Alopecia 100% patients.

Carboplatin: Nausea and vomiting 66% (G1-48%, G2-11%, G3-3%, G4-4%) Neutropaenia 81% (G1-16%, G2-22%, G3-28%, G4-15%) Thrombocytopaenia 72% (G1-21%, G2-20%, G3-23%, G4-8%).

Twenty two patients were evaluable for response, complete response 36%, partial response 36%. The actuarial survival at 18 months is 74% and the regime is well tolerated. Thrombocytopaenia with paclitaxel is uncommon and neutropaenia of short duration. The profile of myelotoxicity of both drugs supports their potential use in combination.

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RESPIRATION INDUCED MOTION OF THE KIDNEYS: IMPLICATIONS FOR BLOCK DESIGN IN WHOLE ABDOMINAL RADIOTHERAPY (WAR)

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Purpose: Whole abdominal radiotherapy (WAR) is frequently used in the treatment of tumors of the ovary and endometrium. The limited radiation tolerance of several critical organs, especially the kidneys, is an important consideration in the design of WAR fields. Although renal blocking is standard for WAR, few guidelines exist in the literature to factor respiration-induced kidney motion into the design of these blocks. *Methods:* Radiographs were obtained to measure kidney excursion under forced respiratory conditions in 6 patients (10 visualized kidneys). Intravenous contrast was administered and AP films were obtained at maximum inspiration and expiration. A horizontal reference line was drawn at the bottom of the L3 vertebral body and the excursion of each kidney was determined relative to this line. The kidney position on the actual treatment simulation film was also determined using this technique. These excursion movements were incorporated into the design of an idealized block to account for all phases of respiration. *Results:* The range of excursion for the left kidney was 1–32 mm and for the right kidney was 3–14 mm. In a worst case scenario, the left kidney block required an additional 14 mm above and 32 mm below the renal silhouette on the simulation film. The corresponding values for the right kidney were 17 mm and 10 mm, respectively. *Conclusions:* Although kidney motion under forced respiratory conditions is not representative of typical treatment conditions, the data highlight the possibility of significant renal movement during treatment. These factors must be kept in mind when customizing renal blocks.

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EVALUATION OF EFFECT OF THE ACTIVE METABOLITE OF AMIFOSTINE (AMI), WR-1065, ON THE CYTOTOXICITY OF ANTICANCER DRUGS AGAINST HUMAN OVARIAN CANCER

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Ami protects normal but not tumor tissue from cytotoxic effects of radiation and chemotherapy. The effect of amifostine's active metabolite, the free thiol, WR-1065, on the cytotoxicity of standard anticancer drugs was tested against human A2780 ovarian cancer *in vitro* using the sulforhodamine B assay for viability. Dose response and IC_{50} values were determined in triplicate for each drug in the presence and absence of the highest nontoxic dose of WR-1065. IC_{50} values (molar conc) for the drug alone and following pretreatment with WR-1065 were: taxol 1.7 vs 1.3×10^{-8}; cisplatin 9.2 vs 3.1×10^{-4}; carboplatin 9.6 vs 8.9×10^{-3}; doxorubicin 5.6 vs 0.08×10^{-4}; mitoxantrone 7.9 vs 0.18×10^{-6}; 5-FU 8.5 vs 8.5×10^{-5}; vinblastine 4.5 vs 3.3×10^{-8}, respectively. The IC_{50} differences $\pm$ pretreatment with WR-1065 were not statistically significantly different. These data expand upon previous reports showing that Ami or WR-1065 does not protect tumors from the cytotoxic effects of anticancer agents. Ami's ability to protect dose-limiting toxicity to normal tissues without protection of tumor should enhance the efficacy ratio of a variety of standard anticancer drugs.