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11.061

UPDATE OF A RANDOMIZED TRIAL OF CISPLATIN (P) AND CYCLOPHOSPHAMIDE (C) ± WR-2721 (WR) IN PATIENTS WITH ADVANCED OVARIAN CANCER

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Cisplatin toxicity often limits optimal therapy of patients with Stage III/IV ovarian cancer. We are conducting a randomized study to determine if pretreatment with WR reduces the toxicities of high dose cisplatin and cyclophosphamide. To date 63 patients have been randomized to WR + CP and 58 to CP. In the WR-containing arm, 5 patients of 63 were admitted to hospital for neutropenic fever/sepsis compared to 15/58 CP patients ($p=<0.01$). There were three additional CP patients who required discontinuation of therapy due to prolonged neutropenia (< 1500/μl) for >2 weeks ($p=0.001$). In the WR-treated patients 11/63 (17.5%) developed hypotension during the WR-infusion which easily and quickly reversed upon cessation of therapy with no sequelae. Of 40 patients who came to second-look laparotomy, pCR was present in 9/19 WR + CP and 8/21 CP patients (NS). Therefore, pre-treatment with WR significantly decreases serious hematological complications and their sequelae without interfering with tumor response in patients with advanced ovarian cancer.

11.062

BINDING SYNERGISM BETWEEN MABS DIRECTED TO AN OVARIAN TUMOR ASSOCIATED ANTIGEN.

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Three mouse MAbs, with tumor-restricted specificity for human ovarian carcinoma, directed against distinct epitopes of the same 38KD molecule, were used in double combination. A temperature-dependent binding synergy was observed with ^{125}I-MOv18 and unlabelled MOv19 MAbs on different cell lines, alive or glutaraldehyde-fixed and on crude membrane preparations. The chimeric version, with the human Fc-region, of the mouse MAbs, as well as monovalent forms as bispecific MAbs (MOv18/CD3 and MOv19/ CD16) deprived of their parental components by HPLC, were also studied. The results obtained by using these reagents in different combinations suggest that the interaction of the Fc regions of the 2 MAbs, which are brought close together by binding to the same antigen, is unlikely. The synergism seems to be due to a conformational change in the 38KD molecule following MOv19 MAb binding. We are now analyzing the biological relevance of the synergism in radiolocalization and in bispecific MAb retargeting of T-cell cytotoxicity.

11.063

LEVELS OF MACROPHAGE COLONY-STIMULATING FACTOR (M-CSF), INTERLEUKIN-1 (IL-1), INTERLEUKIN-6 (IL-6) AND TNF ALPHA IN HUMAN OVARIAN CANCER.

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Ovarian cancer cells have been found to secrete various cytokines. Although the biological relevance of these factors on the progression of the tumor is not completely understood, they may contribute in the regulation of tumor cell proliferation by autocrine and paracrine mechanisms. In the present study, we have determined the levels of these growth factors in serum and ascites fluid obtained from normal controls and ovarian cancer patients. The levels of cytokines were determined by solid phase ELISA and radioimmunoassay. The results indicate that the concentrations of IL-6 was substantially higher in the ascites of ovarian cancer patients. Serum levels of the cytokines did not show any significant difference except for M-CSF, and TNF-alpha . The levels of M-CSF in serum was about three fold higher in ovarian cancer (> 70 %) than normal controls. TNF-alpha levels in serum was significantly higher in primary Ovarian cancer when compared with second look ovarian cancer patients and normal controls.

11.064

CYTOSOLIC PLACENTAL FERRITIN (p43) CONCENTRATION, AND ITS PROGNOSTIC SIGNIFICANCE IN CARCINOMA OF THE BREAST.

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p43, a new protein associated with placental isoferritin (PLF) is measured by CM-H-9 McAb. PLF bound to T cells was previously detected in 95% of patients with early stage bc. In the current study we determined the PLF concentration in bc tissue and correlated its cytosolic level with prognostic indicators. Cytosols were prepared from 122 frozen tumors of patients followed for 5-7 years. PLF was determined by CM-H-9 McAb ELISA. The mean PLF concentration was 32±50 U/mg cytosolic protein. A significant inverse correlation was found between PLF level and tumor size, grade, nuclear pleomorphism and rate of mitoses, and a positive correlation with ER. Patients with PLF more than 8U/mg of cytosolic protein had a significantly longer overall survival than those with lower concentration. PLF is a tumor product with prognostic significance.

11.065

CIS-PLATIN PLUS 5-FU RADIOSENSITIZATION OF HEAD AND NECK CANCER PATIENTS (A PILOT STUDY)

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A pilot study on 31 T2-4 N0-3 M0 head and neck cancer-patients was conducted, to assess the efficacy of the cis-Platin + 5 FU radio-sensitization. A 5-day continuous infusion of 600 mg/m^2 5 FU, followed by 100 mg/m^2 cis-Platin (on the 6th day) was applied, simultaneously with the initiation of the irradiation, with 2 Gy fractions, up to a 30 Gy total dose. After a 20-day pause, the irradiation was continued, with or without sensitization, up to 50-60 Gy total dose. A dramatic tumor response in some 80 % of the patients(30 % CR and 50 % PR) was observed; the rest 20 % showed no response. Compared with 39 control patients, the tumor response showed to be better with the sensitizers. The toxicity of the combination seem to be acceptable. Nevertheless, 40 % of the patients came back with evidence of recurrent disease, some even after a complete response. The study continues.

11.066

The prognostic value of Proliferating Cell Nuclear Antigen (PCNA) expression in early glottic cancer.

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The proliferating cell nuclear antigen (PCNA), auxiliary protein of DNA-polymerase delta, is a proliferation sensitive DNA replication protein maximally elevated in late G1 and S phases of the cell cycle. By the use of murine monoclonal antibodies the expression of PCNA was quantified in histological sections from paraffin-embedded primary diagnostic biopsies from early glottic cancers (Tis, T1) which later were submitted to radiotherapy. Using a quantitative scoring system to evaluate the PCNA positivity it was found that the tumors which recurred after full dose radiotherapy (64Gy) displayed lower PCNA activity than the cured patients. PCNA appears to be one important parameter useful for the biological characterization of the tumor and a contributory tool to identify the 10-15% early glottic cancers which recur after radiotherapy.