954 PUBLICATION

Serum cytokine levels in human papilloma virus (HPV)-related cervical disorders

A. Torresin[1], R. Dalzini[2], G. Tunesi[3], C. Giuliano[4], C. Lorusso[1], G. Penco[1]. *[1]Dpt of Infectious Diseases; [2]Dpt of Obstetrics and Gynecology; [3]Dpt of Pathology; [4]Laboratories of Biochemistry, Galliera Hospital, Genoa, Italy*

Purpose: to assess the difference, if any, between serum levels of interleukin 6 (IL6), tumour necrosis factor alpha (TNFα), c-reactive protein (crp) and ferritin in patients with different HPV-related cervical disorders.

Methods: IL6, TNFα, crp and ferritin were measured (single determination, standard methods) as follows: in 24 pts seen at diagnosis (9 with cervical dysplasia, CIN I–III; 15 with condilomata), mean age 32.5; 11 disease-free pts, mean age 28.2, seen at a follow-up visit for previous dysplasia (5) and condilomata (6).

Results: mean values are plotted in the table.

NV	IL6 pg/ml 3–8.5	TNFα pg/ml 3–20	CRP mg/dl <1	FERR ng/ml 15–155
CIN-D	6.9	18.1	0.4	21.5
CIN-DF	4.6	21.2	0.4	40.9
COND-D	5.4	20.4	0.8	26.2
COND-DF	3.5	17.3	0.6	34.5

(COND = condilomata, D = at diagnosis, DF = disease-free)

No difference was observed by Student's t test among the mean values measured in the 4 subgroups, although there was a slight trend towards abnormal values for crp, IL6 and TNFα in the CON-D pts.

Conclusion: neither in situ cervical cancer nor condilomata secondary to HPV infection seem to induce any significant alteration in the circulating levels of cytokines and acute phase reactants.

955 PUBLICATION

Treatment of endometrial stromal sarcoma

N.I. Lazareva, V.V. Kuznetsov, V.M. Nechushkina. *Blokhin Cancer Center, Moscow, Russian Federation*

Purpose: Different treatment modalities of endometrial stromal sarcoma (ESS) were evaluated.

Methods: 50 patients with ESS were included in the study. The mean age was 46.5 years. Stage I tumor was in 28 (56%) patients, stage II – in 7 (14%), stage III – in 8 (16%) and stage IV – in 7 (14%) patients. Twenty four patients were only operated on. Hysterectomy and bilateral salpingo-oophorectomy were performed. Twenty one patients were applied combined treatment modalities, 13 of them – operation and chemotherapy, 3 – operation and radiotherapy (external radiation to the primary tumor zone and regional nodes) and 5 – operation, chemo- and radiotherapy.

Results: 45 patients were followed up. Five-year disease-free survival was 55.6% and ten-year – 26.7%. Five- and ten-year survival after surgical treatment was 66.7% and 33.4%, respectively, after combined treatment – 42.9% and 19.1%, respectively. The data aren't significant. ESS spread to the ovaries, pelvic lymph nodes and to the omentum in 37.5%, to the para-aortic lymph nodes in 25%, to the vagina in 12.5% of cases.

Conclusion: We consider it's necessary to perform radical hysterectomy and bilateral salpingo-oophorectomy in stage I ESS and radical hysterectomy, bilateral salpingo-oophorectomy, and omentectomy in stage II–III ESS. If there are positive retroperitoneal lymph nodes and if there is spread to the omentum, ovaries, or vagina postoperative radiotherapy and chemotherapy should be applied.

956 PUBLICATION

Monocyte chemoattractant protein-1 serum levels in ovarian cancer patients

L. Hefler, C. Tempfer, G. Heinze, S. Leodolter, G. Sliutz, A. Reinthaller, Ch. Kainz. *Department of Gynaecology, University of Vienna Medical School, Vienna, Austria*

Purpose: To evaluate MCP-1 serum levels in patients with ovarian cancer and to determine its value as differentiation marker and prognostic marker.

Methods: MCP-1 serum levels were determined in 48 patients with primary and 38 with recurrent ovarian cancer, 67 patients with benign ovarian cysts, and 42 healthy women by using a commercially available ELISA.

Results: Median MCP-1 serum levels in patients with primary ovarian cancer, recurrent ovarian cancer, benign ovarian cysts, and in healthy women were 535.6 (range 129.6 to 1200) pg/mL, 427.3 (range 193.4 to 1101) pg/mL, 371.2 (range 222 to 986.8) pg/mL, and 318.7 (range 241.3 to 681.4) pg/mL, respectively (Mann-Whitney U-test, $p < 0.001$). Univariate logistic regression models revealed a significant influence of MCP-1 serum levels on the odds of presenting with ovarian cancer versus benign cysts and versus healthy women, respectively ($p < 0.001$; and $p < 0.001$, respectively). In a multivariate logistic regression model, both MCP-1 and CA 125 revealed statistical significance on the odds of presenting with ovarian cancer versus benign cysts ($p = 0.05$, and $p < 0.001$, respectively). Elevated MCP-1 serum levels prior to therapy were not associated with disease free and overall survival (log-rank-test, $p = 0.2$; and $p = 0.7$, respectively).

Conclusion: MCP-1 might play a role in the natural history of ovarian cancer and might serve as differentiation marker between benign ovarian cysts and ovarian cancer, providing additional information to the established tumour marker CA 125.

957 PUBLICATION

Hypoxic abdominal perfusion plus chemosensitivity guided chemotherapy using ATP-bioluminicence assay as an effective therapy for recurrent ovarian cancers

Herwart Müller, M.D. Zwirner. *Carl von Hess-Hospital, D-97762 Hammelburg; Universitäts Frauenklinik, D-72076 Tübingen, Germany*

In order to increase response rates and improve survival of recurrent ovarian cancer patients we developed new strategies such as isolated hypoxic abdominal perfusion (HAP) to increase locoregional drug concentrations and individualization of chemotherapeutic regimens by using an ATP-bioluminicence sensitivity assay.

Material and Methods: Between 10/94 and 12/98 44 consecutive patients were treated by three different protocols: *Group A:* 11 pts., 2 cycles of HAP using Novantron (20 mg), Cis-platinum (75 mg) and Germanin (2000 mg) as cytostatics. *Group B:* 21 pts., 2 cycles of HAP using Mitomycin (20 mg), Cis-platinum (75 mg) and Treosulfan (7.500 mg) combined with 1 cycle intraaortic infusion of the same drugs. *Group C:* 12 pts., 3 cycles of an individualized treatment plan after chemosensitivity testing using ATP-bioluminicence assay – most drugs were given during HAP procedure.

Results: The three groups were well balance in terms of age, Karnofsky-index, UICC-stage: Group A: 58.1 y, 89.1, III 45%, IV 55%; Group B: 58.2 y, 86.2, III 67%, IV 33%, Group C: 56.3 y, 89.2, III 58%, IV 42%. No specific side effects could be observed. In most cases side effects were mild not exceeding WHO grade II. Remission rates were as follows: A: 45% CR 2, PR 3/11; B: 57% CR 6, PR 6/21; C: 92% CR 4, PR 7/12. The following survival rates after 12 and 24 months could be observed: Group A: 50%, 40%; B: 76%, 57%; C: 100%, 92%. This difference in survival was statisticly significant with p-value <0.00001.

Summary: Hypoxic abdominal perfusion is a therapeutic tool leading to increased regional drug concentrations hight enough to break through resistance in recurrent ovarian cancer patients. The combination of regional chemotherapy and individualisation of chemotherapeutic protocol will lead to an increase in response rate and prolongation of survival. Further studies have to confirm these encouraging results.

958 PUBLICATION

Expression of proteins – Products of genes involved in apoptosis regulation in epithelial tumors of ovarian cancer patients with different sensitivity to anticancer drugs

G. Kulik, L. Lukjanova, O. Yurchenko, L. Vorobjova, V. Chekhun. *R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, Nat. Academy of Sciences of Ukraine, 252022, Kyiv, Ukraine*

Drug resistance represents one of the main reasons of failure in treatment of malignant tumors. Many anticancer drugs affect cancer cells by the induction of apoptosis. We have studied the expression of p53 and bcl-2 proteins affecting apoptosis and p-glycoprotein (product of mdr gene) in cells of epithelial ovarian tumors with different sensitivity to anticancer drugs

The sensitivity of cancer cells to cisplatin, cyclophosphane, thiophosphamide and doxorubicin has been assayed in vitro by the degree of SH-group inactivation in the tissue of the tumors due to the action of these drugs. The expression of the above-mentioned proteins has been studied immunohystochemically by PAP-technique in cryostat sections. The specimens of 20 patients with malignant ovarian cancer of different hystology have been analysed. The p53 expression has been shown in majority of the tumors under study with the most intensive reaction being observed in the cells of the least sensitive tumors. Most tumors do not express bcl-2

protein, moreover bcl-2 expression does not correlates with tumor sensitivity to anticancer drugs. P-glycoprotein expression strictly correlate with tumor resistance to some anticancer drugs.

The data on p53 protein expression in tumor of ovarian cancer patients could be useful for further studies aimed at elaborating the new biological methods allowing us to overcome the drug resistance and to improve the effectivity of chemotherapy in the treatment of ovarian cancer patients.

959 PUBLICATION

Epirubicin (E) + paclitaxel (T) in pretreated advanced ovarian cancer (AOC) patients

J.P. Guastalla, C. Martin, D. Tigaud, D. Dramais, E. Levy, B. Leduc, P. Vincent, D.I. Paraiso, E. Pujade-Lauraine. *For the GINECO Group; Centre Leon Berard, Oncology 2B Nord, 28 rue Laennec, 69373 Lyon Cedex 08, France*

Purpose: Evaluation of activity and tolerance of the ET combination in heavily pretreated AOC patients (pts).

Methods: 34 pts with relapsed AOC were treated with E (75 mg/m^2) followed by T (175 mg/m^2, 3 h) q 3 wks with response (R) evaluation every 2 cycles.

Results: Pt characteristics were: median age 56 (32–70), serous histology (82%), PS 0–1 (90%), ≥2 previous chemotherapy regimens (71%), previous taxane (67%), chemoresistance (55%). Toxicity of the 164 evaluable courses was primarly hematologic (%): grade 3/4 neutropenia (9/77) with neutropenic fever in 10%, grade 3/4 anemia (7/1) and thrombopenia (3/4). Nonhematologic toxicities include alopecia (87%), neurotoxicity (NCI grade 2: 15%) and nausea/vomiting (grade 3–4: 17%). One pt had a drop of LVEF and stopped E. Overall RR is 38% (95% CI = 21–55%) with 7 partial and 2 complete R out 24 pts with measurable lesions and 4/10 serologic R (Rustin criteria). Efficacy was independent of resistance to previous treatment. The median time to progression and median global survival were respectively 27 and 51 weeks.

Conclusion: the epirubicin-paclitaxel combination has a high activity in heavily pretreated AOC patients and merits testing in first line therapy.

960 PUBLICATION

Cisplatin-docetaxel (Taxotere®) in first line treatment of advanced ovarian cancer (AOC)

V. Dieras, J.M. Ferrero, R. Kheder, B. Weber, P. Winckel, A. Lortho-lary, F. Mayer, D.J. Paraiso, E. Pujade-Lauraine. *For french GINECO group; Institut Curie, Oncology, 26 rue d'ULM, 75231 Paris Cedex 05, France*

Purpose: Evaluation of tolerance and efficacy of Taxotere® (T) with cisplatin (C) in first line treatment of advanced AOC.

Method: From 03 to 11/97, 45 patients (pts) with FIGO stage III/IV OC, a median age of 56 (range = 39–69) and macroscopic residual disease (<1 cm = 14 pts, ≥1 cm = 31 pts) were treated by 6 courses (co) q 3 weeks of T 75 mg/m^2, I.V., followed by C, 75 mg/m^2, I.V. Oral premedication combined a 5-day regimen of prednisolone 50 mg bid and continuous diosmine 1 g bid. Efficacy evaluation was based on results of second look laparotomy (SLL) and time to progression (TTP)

Results: The 6 co were completed by 40/44 evaluable pts (91%). Co delay (≥7 d) was observed in 15/259 (5%). Dose-intensity was 98% respectively for T and C. Main toxicity was neutropenia: NCI grade 3/4 in 110 co (45%) and 36 pts, with febrile neutropenia (2 pts), but no use of G-CSF. Grade 3/4 anemia and thrombopenia were observed in respectively 2 and 0 co. Nonhematologic toxicities were alopecia (gr 2: 75%), nausea/vomiting (gr 3/4: 16%), edema (gr 2: 7%, 3: 4%), cutaneous (gr 2: 7%), neurologic (any gr: 26%, gr 2: 4%). At SLL (43 pts), pathologic CR and microscopic residual lesions were found in respectively 21% and 29%. Median TTP was 16 months.

Conclusion: the low rate of neurologic toxicity and severe thrombopenia make cisplatin-taxotere a valuable platin-taxane combination in AOC therapy.

961 PUBLICATION

Maturation of dendritic cells (D.C.) from ovarian cancer patients

E. Zavadova[1], C. Savary[2], R.S. Freedman[1]. *[1]Department of GYN/Oncology; [2]Department of Surgery, M.D. Anderson Cancer Center, Houston, TX 77030, United States*

Dendritic cells are the most potent antigen-presenting cells of the immune system. We have shown that D.C. from ascites of patients with peritoneal carcinoma have low maturity (Clin Cancer Res 4:799–809, 1998). Here we examined the effects of the *in vitro* treatment of D.C. with cytokines or proteolytic enzymes papain, trypsin and chymotrypsin (polyenzyme preparation Wobe-Mugos®, Geretsried, Germany) on the phenotype and function of D.C. This preparation has been used successfully in a additive therapy of some cancer patients. D.C. from ascitic fluid of 16 untreated ovarian cancer patients were cultured either with RPMI medium alone or with medium containing granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor alpha (TNF-α) and interleukin-4 or with medium containing Wobe-Mugos) for 5–7 days. After washing, phenotypic analysis of cells on culture day 7 showed that D.C. cells expressed higher proportions of CD83$^+$, CD40$^+$ and CD80$^+$ cells when incubated with cytokines or enzymes than D.C. incubated only with medium alone. Mixed lymphocyte reactions resulted in stimulation of allogeneic T-cells. This investigation shows that D.C. from peritoneal cavity of patients with untreated ovarian cancer can be maturated. This may be of relevance for the modulation of D.C. functions in cancer patients by therapeutic measures. (Supported in part by MUCOS Pharma).

962 PUBLICATION

Docetaxel (D) and carboplatin with Auc-7 as first-line chemotherapy in advanced epithelial ovarian cancer

Mehrdad Salimi, Manuchehr Davaee. *Iranian Cancer Institute, Tehran, Iran*

To determine the response rate and toxicity of Docetaxel/Carboplatin regimen as first line treatment in advanced epithelial ovarian cancer, an open, non- randomized and prospective clinical trial was designed.

Materials and Methods: from Feb. 1996 to Dec. 1997. 28 Patients were included. Docetaxel 75 mg/m^2 i.v as a one hour infusion followed by Carboplatin at Auc 7 was given every 21 days for a total of 6- cycls. Mean age was 50 years. Stage 3:18 pts (64%), stage 4:10 pts (35%). After 6 cycles of chemotherapy clinical response was evaluated and 2nd. look laparatomy was performed in all 10 patients who achieved C.R. The clinical response was assessed by radiological methods and serum CA- 125 levels.

Results: CR: 10/28 (35%), PR: 16/28 (57%), SD: 2/28 (7%). The overall RR was 26/28 (92%). After 2nd-look laparatomy in 10 pts the following results obtained. Pathologic CR was observed in 4/10 (40%) and Pathologic PR in 5/10 (50%). One patient was found to have unresectable disease at 2nd look laparatomy.

Toxicity: Neutropenia G-3: 2 (7%), thrombocytopenia G-3: 2 (7%), G-4 hematologic toxicity was not observed. Mucositis G-3: 1 (3.5%), neurotoxicity G-2 10 (35%) and neurotoxicity G-3: 2 (7&). No grade 4 non-hematologic toxicity observed.

Conclusion: this combination is very active in epithelial ovarian cancer with acceptable toxicity profile.

963 PUBLICATION

Consolidation radiotherapy following cytoreductive surgery, chemotherapy and second-look laparotomy for epithelial ovarian carcinoma: Long-term follow-up

M.E. Stein, H. Goldberg, E. Toffler, N. Menashe, M. Steiner, D. Beck, A. Kuten. *Department of Oncology, Rambam Medical Center and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*

Introduction: From 1979–1987, 139 Stages IC-IV ovarian cancer patients (pts) who had undergone cytoreductive surgery received 6–11 cycles of cisplatin + adriamycin. Eighty-four clinical complete responders underwent second-look laparotomy (SLL), 60 of whom received consolidation abdominal irradiation.

Results: After a median follow-up of 39 months (m), the ten-year actuarial survival figures were: all pts – 24%: no residuum at primary surgery – 35%: residual tumor <2 cm – 35%: residual tumor >2 cm – 4%. Mean survival of irradiated Stages III–IV pts with negative SLL: 31.9 ± 2.8 m, compared to 25.9 ± 4.5 m in non-irradiated pts and 35.6 ± 2.7 m in irradiated pts with microscopic disease at SLL (p = 0.04).