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

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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)

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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

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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

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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

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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).

Conclusions: Despite the initial survival advantage observed in irradiated pts, due to late recurrences there was no significant difference in the long-term survival probability of non-irradiated pts. Consolidation whole abdominal irradiation in advanced stages of ovarian cancer may be of value in pts with negative or microscopic disease at SLL.

964 PUBLICATION

Treatment of recurrent ovarian cancer: Intraperitoneal mitoxantrone plus vinorelbine i.v. versus mitoxantrone i.v plus vinorelbine i.v.

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Purpose: To evaluate whether intraperitoneal administration of Mitoxantrone offers any advantage over I.V administration.

Methods: Thirty two (32) women of mean age 65.27 ± 5.13 years with recurrent ovarian cancer were evaluated after treatment (Group A n = 13) with Mitoxantrone (Novantrone, Wyeth-Lederle) intraperitoneally – 36 mg/m" day 1, every 21 days × 6 cycles- plus Vinorelbine i.v. (Navelbine Pierre Fabre) – 37.5 mg/m" day 1 and 8, every 21 days × 6 cycles- or (Group B n = 19) with Mitoxantrone i.v.- 14 mg/m" day 1 every 21 days × 6 cycles – plus Vinorelbine i.v. – 37.5 mg/m" day 1 and 8, every 21 days × 6 cycles.

Results: Response was observed in 6 patients (46.15%) of Group A and in 12 patients (63.15%) of Group B, but this difference was not statistically significant (p = 0.07). There were observed 3/3 pCR in Group A and 6/7 pCR in Group B (p = 0.507). The overall 28 months survival was 76.92% for Group A and 73.68% for Group B (Kaplan-Meier method p = 0.642)

Conclusions: The intraperitoneal administration of Mitoxantrone does not increase the response rate and the overall survival in patients with recurrent ovarian cancer.

965 PUBLICATION

Topotecan (TPT)-based salvage chemotherapy in advanced epithelial ovarian cancer (EOC): A randomized study

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Purpose: In vitro enhanced activity of TPT when combined with Cisplatin (DDP) has been reported. We evaluated the efficacy of TPT vs. TPT + DDP in salvage therapy of EOC after at least 2 lines of chemotherapy contaning DDP and Paclitaxel in a prospective randomized study.

Methods: 18 Pts have been enrolled. 10 Pts received TPT + DDP (TPT 0.5 mg/sqm/day d.1–5 + DDP 50 mg/sqm d.5 q.3 weeks) and 8 had TPT (1.25 mg/sqm/day d.1–5 q.3 weeks). Treatment was repeated when Absolute Neutrophil Count > 1500/mcl and Platelets > 100000/mcl:

Results: In TPT + DDP arm (41 courses) there were 2 grade 3 and 1 grade 4 neutropenia and 2 grade 3 thrombocytopenia; 1 delay of treatment. Out of 10 evaluable pts we had 3 partial responses and 4 stable disease (time to progression 23 weeks, range 9–45).

In TPT arm (27 courses) we observed 8 grade 3 and 4 grade 4 neutropenia, 3 grade 3 and 1 grade 4 thrombocytopenia; 1 delay of treatment. Out of 7 evaluable pts we had 1 partial response and 1 stable disease (time to progression 16 weeks, range 4–28).

Conclusions: DDP + TPT combination seems a very promising schedule worthy of further investigations. Other dose regimens and higher TPT doses may be tested. The study is ongoing.

966 PUBLICATION

Low neurotoxicity of chemotherapy with Carboplatin/Docetaxel for reccurent epithelial ovarian cancer

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The high incidence of peripheral neurotoxicity (PNT) in cisplatin-based chemotherapy for ovarian cancer is often a limiting factor for platinum-reinduction in the case of relapse. Substituting carboplatin for cisplatin in first-line therapy has been shown to decrease the incidence of neurologic and other non-hematologic toxicities without significant difference in tumor response.

In a pilot study, we sought to evaluate the toxicities of a combination of carboplatin and docetaxel in 16 women with relapse of ovarian carcinoma >6 months after completion of first-line platinum-based chemotherapy.

Pts. received carboplatin (AUC5) and docetaxel (75 mg/m^2), i.v., q21. A total of 86 courses was applied. Apart from alopecia, predominant toxicity was hematologic, with WHO grade 2/3 leukopenia in 13/16 and thrombocytopenia in 3/16 pts. Grade 3 PNT was not observed, grade 2 PNT occurred in 1/16 and grade 1 PNT in 12/16 women. 12/16 pts. suffered from mild nausea and vomiting (WHO 1/2), 4/16 from light to moderate fluid retention. Almost all pts. complained of painful, often infectious, changes of finger- and toenails. Ototoxicity and nephrotoxicity were not observed.

9/16 pts. achieved remission with therapy, 2 pts. had NED, 3 pts. stable disease. Five women relapsed within 2 to 9 months after therapy, 2 women progressed under treatment. More complete follow-up data will be available 9/99.

In summary, combination chemotherapy with carboplatin/docetaxel seems an effective treatment for relapse of ovarian carcinoma. Toxicities, especially PNT, tend to be less severe than with cisplatin/paclitaxel. These results warrant larger studies to assess the feasibility of platinum/taxane reinduction for epithelial ovarin cancer with this regime.

967 PUBLICATION

Prognostic significance of heat shock protein (HSP72) immunostaining in epithelial ovarian carcinomas

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Purpose: To evaluate the prognostic value of Heat Shock Protein (HSP) expression in ovarian carcinomas. The correlation between the expression of this protein and the disease parameters: FIGO stage, histological type, tumour differentiation and steroid hormone receptor status (ER, PR) was investigated.

Patients and Methods: One hundred imprint smears from ovarian carcinomas specimens were studied using immunocytochemical techniques. Twenty nine patients were with stage I, 24 with stage II, 40 with stage III kai 7 with stage IV disease according to the FIGO classification.

Results: The sensitivity and specificity of HSP for malignancy was 37% and 90% respectively. HSP was statistically significantly associated with malignant tumours (x^2 = 4.3, p < 0.05) and undifferentiated carcinomas. The relationship of HSP with malignant tumours is confined to the premenopausal group of patients (x^2 = 13.2, p < 0.001).

Conclusion: It can be stated that there is a positive association between HSP positivity in premenopausal patients with malignant ovarian tumours and especially with histologically undifferentiated ovarian carcinomas.

968 PUBLICATION

TNF profiles in ovarian cancer and their response to anticancer therapy

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Purpose: The increased TNF level in biological fluids in ovarian cancer patients has been described earlier. However the contribution by different host and tumor cell populations in general serum and ascite fluid TNF level is not clear, as well as their changes during anticancer chemotherapy.

The TNF levels in ascite fluids, serums, supernatants of 24 h primary ovarian cancer cultures, supernatants of ascite associated peritoneal macrophages (Mp) and peripheral blood lymphocytes (PBL) in 32 cancer patients were determined before any treatment with bioassay using sensitive transformed fibroblasts L-929 cell line. The same parameters were analyzed in 17 ovarian cancer patients after 3–4 cycles (cis-pla-tinum –75 mg/m^2 and cyclophosphomide 750 mg/m^2) preoperative chemotherapy (CT)

Results: TNF serum level was significantly higher in the group with preoperative CT – 0.54 ± 0.08 ng/ml than in serum samples in nontreated patients (0.23 ± 0.03 ng/ml, p ± 0.05). There was the trend to enhance of TNF production by peritoneal Mp after CT (0.32 ± 0.07 ng/ml in treated group and 0.28 ± 0.09 ng/ml in nontreated patients). At the same time common TNF level in ascite fluid was higher in nontreated patients (0.37 ± 0.08 ng/ml) than in group after CT (0.22 ± 0.03 ng/ml). CT decreased the