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DIFFERENCES IN ACTIVITY OF MITOXANTRONE (DHAD) PLUS IFOSFAMIDE (IFO) ACCORDING TO PREVIOUS PLATINUM-COMPOUND (PC) RESPONSIVENESS IN ADVANCED OVARIAN CANCER (AOC). AN I.T.M.O. GROUP STUDY.

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Previous studies have suggested that DHAD and IFO, given in monochemotherapy to AOC patients previously treated with PC, induce 15-20% tumor responses. In an attempt to improve these results by associating both drugs, 62 pts were treated with the combination: 49 are evaluable, 13 being still on treatment. Median age was 57, PS 0/1 in all cases. Responsiveness to previous treatment with PC was as follows: sensitive (PC+) 18 pts, resistant (PC-) 23 cases, undetermined 8 pts. Disease volume at study entry was: measurable lesions (ML) 30 pts, clinically undetectable disease 19 pts. DHAD (10 mg/m^2) and IFO (4 g/m^2) were given i.v. on day 1 and recycled on day 21. In the case of CR or PR, treatment was continued; otherwise it was stopped after 6 cycles. In the 30 pts with ML, 7 responses (1 CR) were observed, with a median duration of 4 mos. Median time to progression (TTP) for the 49 pts was 6 mos. Evaluation of activity according to PC responsiveness:

	PC+	PC-
No. responses (CR+PR)	6/13 (46%)	1/17 (6%)
Median TTP(mos)	9	5

Treatment was well tolerated: 8/49 pts had grade III leukopenia, and 2/49 grade III vomiting. Our study shows that DHAD+IFO has a certain degree of activity in PC+ pts and no efficacy in PC- pts. It is suggested that new drugs for Phase II studies in AOC should be first evaluated in PC- pts; in this way it might be possible to identify compounds not cross-resistant with PC.

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LONG-TERM RESULTS OF SURGERY AND CISPLATIN-BASED CHEMOTHERAPY IN ADVANCED EPITHELIAL OVARIAN CANCER

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In patients (pts) with advanced ovarian cancer, cisplatin-based chemotherapy (CT) is generally accepted to be the treatment of choice after debulking surgery. This report deals with the long-term results of such a therapy in 39 pts who were treated in our institution between 1980 and 1988. The median age was 50 yrs (range 21-71). 13% of pts had stage II, 62% stage III, and 25% stage IV disease. Histologic subtypes were as follows : serous 80%, mucous 10%, clear-cell 2.5%, endometroid 2.5%, and unclassified 5%. After debulking surgery, residual tumor of more than 2 cm was present in 54% of pts, and clinically measurable disease in 51%. CT consisted of cisplatin and cyclophosphamide with or without doxorubicin and/or hexamethylmelamin in 87% of pts and carboplatin together with cyclophosphamide or etoposide in 13%. A median number of 6 CT cycles was given at 4-week intervals. The median dose of cisplatin per CT cycle was 68 mg/m^2. In 20 pts with clinically measurable disease, 12 (60%) objective responses were seen including 10 (50%) clinical complete responses (CCR). For the 10 pts with CCR and the 19 pts with clinically non-measurable disease after primary surgery, the median disease-free survival (DFS) is 33 months, and the probability of DFS at 10 yrs 45%. 19 of these 29 pts underwent a second-look-laparatomy (SLL). In 10 pts, no residual tumor was found, and in another 3 pts, residual tumor was totally resected. Thus, 13 out of the 19 pts (68%) were classified as pathological CR (PCR). In these 13 pts, the median DFS has not yet been reached with a median follow up of 42 months, and the probability of 10-yr DFS is 54%. There is no significant difference in DFS and survival, however, between the 19 pts who underwent SLL and the 10 pts who did not. For the whole group of pts treated, the median survival is 44.5 months and the estimated 10-yr survival 31%. Residual Tumor of less than 2 cm after debulking surgery and serous histology both seem to correlate independently with longer survival and DFS.

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INTRAPERITONEAL ADMINISTRATION (I.P.) OF INTERFERON-a (IFN-a) IN PATIENTS WITH OVARIAN CA, IN CLINICAL COMPLETE REMISSION (cCR) FOLLOWING CHEMOTHERAPY WITH HIGH DOSES OF CARBOPLATIN (C) AND HAEMOPOETIC GROWTH FACTORS (H.G.F.)

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Purpose of the trial is to study firstly the efficacy and the toxicity of H.D. of C+H.G.F. in pts with ovarian CA and secondly the feasibility and the influence on survival of the I.P. administration of IFN-a in pts with cCR after chemo. 35 Pts have been studied. The schedule is C:600mg/m^2, D1 and H.G.F. 5mcg/kg, s.c., D2-14, q 3 w X 6. The pts with cCR were randomized to I.P. IFN-a 25X10^6 U q 2 W X 12, or observation. The median age was 55 years, the P.S. 0-1 in 27/35 and the stages IC 1, II 3, III 24 and IV 4 pts. They received 1-6 cycles of chemo (intesification of doses 88,7%). 24 were evaluated. 17/24(71%) were in cCR and 4(17%) in PR. 13/17 continued with IFN-a. The main toxicity from the chemo was haematological, with median Hb=10,2, WBC=4,0, Neut=2,3 and PLT=173.000. The main side effect of IFN-a was chills and fever.
CONCLUSION: The administration of H.D. of C+H.G.F. is effective with moderate toxicity. The I.P. administration of IFN-a is feasible and well tolerated. Survival data has not yet been completed.

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SECOND-LINE CHEMOTHERAPY WITH MITOMYCIN-C (MM-C) AND 5-FLUOROURACIL (5-FU) FOR OVARIAN CANCER

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The primary treatment for epithelial ovarian cancer is platinum based combination therapy, but in the case of relaps no consensus regarding the optimal therapy exists. Sixteen patients who had previously received platinum-based combination chemotherapy and who had measurable recurrent disease were treated with MMC- 10 mg/m^2 bolus every 6 weeks and 5-FU 1000 mg/m^2 as a continuous infusion for 3 days every 3 weeks. The duration of a treatment cycle was 6 weeks. No responses were seen, 13 patients had progressive disease (PD) and 3 patients were in no change (NC) when they went off study. Median number of courses was 2 (1-4). Median survival was 6 months (3,5-8,5+). Toxicity was manageable, grade 3 myelotoxicity (WHO) was seen in 5 courses, grade 3 nausea and/or diarrhoea in 3 courses.
Conclusion : the present study was unable to show any effect from MM-C and 5-FU in ovarian cancer in patients previously treated with Cisplatin based chemotherapy.

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CARBOPLATIN, CISPLATIN AND CYCLOPHOSPHAMIDE (C.C.C) AS A FIRST LINE CHEMOTHERAPY IN STAGE IIIC EPITHELIAL OVARIAN CANCER

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Ten patients with stage IIIC epithelial ovarian cancer have been included in a feasibility study of first-line chemotherapy with carboplatin 200mg/m^2 day 1, cisplatin 60mg/m^2 day 2, and cyclophophamide 550mg/m^2 d1,2 q 4 wk. After 6 cycles all patients with clinical complete response (cCR) underwent second look laparotomy (S.L.L). There were 2 clinical partial responses and 8 clinical complete responses. Eight patients underwent S.L.L. One patient had residual macroscopic disease greater than 2cm. Three patients had residual macroscopic disease less than 2cm, and 4 patients had macroscopic complete response, 3 of them with pathologic complete response. Toxicity was substantial but manageable. All patients completed 6 courses of chemotherapy. C.C.C regimen can be given safely and preliminary results seem promising.

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CYCLOPHOSPHAMIDE, DOXORUBICIN AND CISPLATIN (CAP) AND SECOND LOOK FOR ADVANCED OVARIAN CANCER

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From october 1983 to july 1990, 33 patients (pts) with stage III-IV advanced epithelial ovarian cancer were treated, after debulking surgery, with chemtheraoy (CAP) for 6 cycles and second look (SL) laparotomy. In the deboulking surgery, the disease not could be resected in 21 pts. When the resection could be possible, the residual disease was greater than 2 cm in 5 pts. In 7 pts, the residual tumour was minor than 2 cm.Following the first 6 cycles, the response was asseable by SL in 25 pts (75,8%) and by clinical parameters in 8 pts (25,3%). Pathological complete response (PCR) rate was 24%(8 pts). Seven pts (21%) had partial response (PR) and they reached complete response (CR) with SL. Ten pts (32%) had PR but they not could obtain CR with SL. Nine pts (27%) progressed (P).
The overral median survival (MS) was 26 months. Pts with PCR had MS of 43 months and pts with CR in the SL of 36 months. The MS was 18 months in pts winth PR. The group of P had MS of 4 months. There was no statistically significant difference in the survival of the PCR and CR with SL group neither betwen pts with CR and PR. However there was a significant difference in the survival PCR and PR (p<0,05) and betwen PR and P (p<0,001).
Pts with CR after SL gad a lower MS than pts with a PCR. However, this difference was not statistically significant. Although pts with PR did not reach CR with SL they had a significant better MS.