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The use of docetaxel in continuous hyperthermic peritoneal perfusion chemotherapy (CHPPC) for peritoneal recurrence of gynecological malignancies resistant to systemic chemotherapy. A feasibility and pharmacokinetic study

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Purpose: Patients with early recurrence or persistent peritoneal disease after systemic chemotherapy for gynecological malignancies have a very poor prognosis. Cytoreductive surgery with CHPPC is a relatively new multimodality treatment used for primary and secondary peritoneal malignancies. We studied the feasibility and pharmacokinetics of docetaxel in CHPPC.

Methods: Fourteen patients, with a mean age of 65 years (51-80) and treated by systemic chemotherapy for gynecological malignancies, mainly ovarian cancer, who demonstrated early peritoneal recurrence or persistent peritoneal disease in the absence of haematogenous metastases, underwent cytoreductive surgery and subsequent CHPPC with 75 mg/m2 docetaxel at 41-430C. One patient was treated twice with CHPPCwith docetaxel. During the first 5 days after intraperitoneal administration, peritoneal fluid and blood samples were obtained for pharmacokinetic analysis.

Results: Two treatment-related deaths were noted (mortality rate: 13%). Other complications, mainly minor, were recorded in 67% of cases. The maximal intraperitoneal versus plasma concentration ratio ranged from 17 to 95, while the intraperitoneal versus systemic exposure ratio varied between 105 and 555. After a median follow-up period of 50 months 8 patients are alive. The peritoneal recurrence rate was 33%. The 1-, 2- and 3-years survival rates were 69%, 62% and 45% respectively.

Conclusions: The use of docetaxel in CHPPC following cytoreductive surgery for peritoneal carcinomatosis from gynecological malignancies resistant to systemic chemotherapy is feasible. Intraperitoneal administration of docetaxel results in a high intraperitoneal versus systemic exposure ratio. It seems that this treatment regimen may contribute to improvement of loco-regional disease control and survival.

Ovarian tumours

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Cyclophosphamide dose intensification with filgrastim support in first line cep regimen in advanced ovarian cancer (AOC): a gineco phase III study

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Purpose: ICON-3 trial preliminary results have suggested that CAP regimen or carboplatine alone may be equivalent to carboplatine-paclitaxel in treatment of AOC patients (pts). CAP regimen, thus, remains an alternative in first line AOC therapy. The GINECO explored the impact of increased doses of cyclophosphamide (Cy) supported by filgrastim (F) in a modified CAP regimen upon FIGO stage III-IV epithelial AOC patients in terms of disease-free (DFS) and overall survival (OS).

Methods: From 02/1994 to 06/1997, 164 pts were randomized to receive 6 cycles every 3 weeks of either standard CEP (S) combining Cy, 500 mg/m2, epirubicin (E) 50 mg/m2, and cisplatinum (P) 75 mg/m2 or intensive CEP (I) with E and P at same doses, but with Cy at 1800 mg/m2 and F (5 μg/kg/d x 10 days). Response was evaluated by second look surgery.

Results: Pts characteristics were well balanced between S and I: median age (60, 59 yrs), per cent of serous histology (69, 67), grade 2-3 (59, 61), PS 0-1 (85, 85) and post-operative residual lesion size: FIGO stage III microscopic (14, 10), <2 cm (30, 31), ~2 cm (34, 40), stage IV (22,19). Final analysis included 155 evaluable pts. Except for grade 3-4 neutropenia (S: 54, I: 38% of cycles), toxicity was superior in I (S, I, %): infection requiring antibiotics (2, 10), grade 3-4 thrombocytopenia (4, 17), anemia (10, 23), nausea-vomiting (38, 48% of pts), diarrhea (0, 5), mucositis (0, 3). Median follow-up is 50 months. Surgical complete response (32%, 15%), DFS in months (16, 15) and OS (35, 30) were not significantly different between S and I.

Conclusion: Increasing Cy dose by more than 3 times with F support in a CEP regimen leads to more toxicity but not to better efficacy in AOC.

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Results from conservative surgery in patients with epithelial ovarian cancer (EOC)

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Aim: Assessing clinical outcome and fertility in patients treated conservatively for EOC from 01/82 to 12/99.

Patients: n = 30; median age: 24 years (15–39); nulliparity: 23; history of infertility: 3 (2 ovulation inductions). Histology: mucinous (63%), endometrioid (20%), others (17%). Tumor grade (Gr): Gr 1 (43%), Gr 2 (57%).

Treatment: Staging surgery (S) was performed in 28 pts, either during initial S (2 pts), or by reassessment S (RS) less than 2 months after initial S (25 pts), or after chemotherapy (CT) (1 pt). Five pts underwent hysterectomy during RS (multiparity (4 pts), extra-ovarian disease (1 pt)). 9 pts received platinum based-CT: stage > IA: 4 pts, stage IA Gr 2 (tumor size $\geq$ 20 cm): 4 pts, stage IA Gr 1: 1 pt (outside our Institut).

Results: Among the 25 pts treated conservatively, final staging distribution was: 19 stage IA (Gr 1 n = 9; Gr 2 n = 10); 1 stage IC, 2 stage II and 3 unknown stages (no RS in 2 pts, RS after CT in 1 pt). Median follow-up: 47 months (6–201). Seven pts relapsed (median time: 15 months (8–51)), 5 on the remaining ovary. The 5-year OS and DFS were respectively, for the 25 pts, 82% and 64%, and for the 19 pts with stage IA disease, 90% and 80%. In stage IA the 5-year DFS was 89% and 71% respectively in Gr 1 and Gr 2 tumors. All pts with stage > IA relapsed. 4 pregnancies only were obtained (1 following *in vitro* fertilization procedure).

Conclusion: Conservative surgery for pts with EOC can be considered in young pts with stage IA Gr 1 disease adequately staged. This procedure must not be performed in pts with FIGO stage > IA.

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Re-induction therapy with paclitaxel and carboplatin in recurrent epithelial ovarian cancer (EOC)

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Purpose: To evaluate the treatment results and toxicity of a re-treatment regimen of paclitaxel and carboplatin in patients with EOC relapse.

Methods: Retrospective study of 241 consecutive patients with primary EOC receiving paclitaxel and a platinum-analogue as first-line treatment after initial staging operation. Inclusion criteria: histologically confirmed FIGO IC - IV EOC; clinical response to first-line treatment; relapse treatment with paclitaxel 175 mg/m2 over 3 hours followed by carboplatin (AUC5), q3w.

Results: 45 patients were included. Time to recurrence from end of first-line chemotherapy was median 14.5 months (range 4.7–41.7 months). Overall response rate was 82% (95% CI: 66.5–92.5%). The progression-free survival and overall survival from start of relapse treatment was median 9.3+ (range 1.3–26.9+) and 11.5+ (range 1.3–35.5) months. In a multivariate Cox analysis, independent prognostic factors for progression-free survival after first relapse were: response to relapse treatment (p = 0.005, HR = 4.85), performance status at time of relapse diagnosis (p = 0.029, HR = 3.84) and time to first recurrence > 12 months (p = 0.030, HR = 0.42). The planned relapse treatment was accomplished by 62% of patients. Doses of paclitaxel and carboplatin were reduced because of hematologic toxicity G3–4 in 13% and 18% of patients, respectively. Only 1 patient had her paclitaxel dose attenuated because of neurotoxicity G3. Hypersensitivity reactions to paclitaxel (n = 4) and carboplatin (n = 5) were observed. Seven patients (15%) had cumulative hematologic toxicity including repetitive episodes (median: 3 [range 2–8]) of prolonged hematologic nadir and/or accumulated cases of hypersensitivity reactions.

Conclusion: Re-induction therapy with paclitaxel and carboplatin in recurrent EOC yielded high response rate and encouraging progression-free survival and overall survival. The therapy is generally well tolerated and toxicity manageable even a small subset of patients had considerable toxicity.