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A phase II trial gemcitabine and cisplatin combination chemotherapy in advanced epithelial ovarian cancer with bulky residual disease

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Purpose: The purpose of this study was to evaluate the efficacy and toxicity of combination of gemcitabine and cisplatin as first line chemotherapy in advanced ovarian cancer with bulky residual disease.

Method: From June 1999 to November 2000, 34 patients were enrolled in this study. Patients with histopathologically confirmed FIGO stage III c and IV disease with residual tumour of more than two centimetres in one dimension after primary cytoreductive surgery were included. No prior chemotherapy, radiotherapy or hormone therapy was allowed. Other eligibility criteria included KPS * 70%, adequate hepatic, renal and marrow function. Median age was 48 years with a range from 26 to 70 years. Twenty-six patients were FIGO stage III c and 8 were stage IV. Gemcitabine was administered as thirty minutes IV infusion on D1 and D8 of 21-day cycle at a dose of 1250 mg/cm2. Cisplatin was given as 75 mg/m2 on D1 only. Common toxicity criteria was used for grading of toxicity and modified WHO criteria was used for response evaluation.

Results: All the Thrity-four patients were evaluable for toxicity and 30 patients were evaluable for response. Grade III/IV toxicities were not seen. Grade I/II leukopenia occurred in 10 patients (29.4%). Grade I/II thrombocytopenia was seen in 4 patients (11.8%). Grade I/II anaemia was seen in 5 patients (14.7%). Grade I/II nausea/vomiting was seen in 5 patients (14.7%). Grade I alopecia was seen in 9 patients (26.5%). Grade I elevation in serum creatinine was seen in 2 patients (5.9%). No rash or flu like symptoms were observed. Complete response was seen in 8 patients (26.7%) while partial response achieved in 15 patients (50.0%) with an overall response rate of 76.7%. Progressive disease was seen in out patient (3.3%) while stable disease was noted in 6 patients (20.0%).

Conclusion: It is concluded that this dose and schedule of gemcitabine plus cisplatin combination chemotherapy has been effective and safe as first line chemotherapy in advanced epithelial ovarian cancer and has given a high overall response rate.

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High dose (HD) topotecan (TPC) with peripheral blood stem cell (PBSC) support in ovarian carcinoma (OC): a phase I study (ITOV 01 protocol)

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Refractory/relapsed OC and FIGO stage IV OC is associated with a poor prognosis. 2nd-line chemotherapy after taxanes/platinum-compounds yields a response rate in the order of 20%.

Rationale: TPC is often used in 2nd-line chemotherapy. A conventional administration (adm; 30'/d x 5d) induces mainly hematological toxicity. A 5d continuous infusion (CI) induces grade IV mucositis [maximum tolerated dose (MTD) <12 mg/m2]. A one-day single adm does not allow more than 10.5 (24-hour CI) or 22.5 mg/m2 (30' adm).

Protocol: We decided to build a HD chemotherapy regimen supported by PBSC with increasing doses of TPC until the MTD. TPC was planned to be administered as a 30' daily perfusion for 5 d, beginning at 4.0 mg/m2/d. Subsequent dose levels were planned as follows: 5.0, 5.5, 6.0, 6.5, 7.0 mg/m2/d. Three pts were to be treated at each dose level. DLT was defined as one toxic death, grade (G) 4 non-hematological tox or G4 hematological tox lasting >6 weeks. In the event of DLT being experienced, a further 3 pts were to be recruited at that dose level. Mobilization to collect 6x10 6 CD34+/kg (a 2nd course was optional) was performed with cyclophosphamide + filgrastim. Considering the good tolerability at 7.0 mg/m2/d (35 mg/m2), we decided to test higher doses: 7.5, 8.0, 8.5, 9.0, 9.5, 10 mg/m2/d.

Results: From 06/98 to 12/00, 29 pts previously treated with platinum/taxane (refractory disease14 pts, early relapse - within 6 months of therapy - 7 pts, FIGO IV OC 8 pts) were included. 28 pts have completed the 1st course, and 9 pts have received 2 cycles. Main tox was G2/3 fever at time of adm for 14 & 3 pts. No G3 diarrhoea was observed. One pt treated at a dose of 35 mg/m2 died of G4 sepsis. One pt had G4 vomiting. No other G4 tox. was observed. Duration of G4 neutropenia/thrombocytopenia were 11d & 7d. Pharmacokinetic data (Cmax, AUC) for 15 pts (at d1-2-5) were linear within the dosing ranges of 4 to 7.5 mg/m2/d. The study is ongoing at a dose level of 8.0 mg/m2/d

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Phase II study of paclitaxel (taxol, gemcitabine, and cisplatin for patients with advanced ovarian cancer)

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Background: Platinum-based chemotherapy, following debulking surgery is the cornerstone in the treatment of advanced ovarian cancer, while the introduction of the taxanes has been a major contribution in the treatment of these patients, both in first as in second line. Gemcitabine induces anti-tumour responses in second-line treatment of ovarian cancer and shows synergism with cisplatin in preclinical studies. For these reasons we performed a phase II study combining these three agents for patients with advanced ovarian cancer, both in primary as in recurrent disease.

Patients and Methods: Treatment consisted of paclitaxel 150 mg/m2, cisplatin 75 mg/m2 on day 1, and gemcitabine 800 mg/m2 on day 1 and 8, followed by rhG-CSF (Filgrastim) 300mg sc. from days 2 to 7. Treatment was repeated every three weeks. Patients had histologically verified epithelial ovarian cancer, FIGO stages IIb, IIc, III, IV or recurrent disease, age between 18 and 70 years, PS was 0,1 or 2, and no brain metastases or demonstrated resistance against cisplatin. The planned number of TGC cycles was 6, starting within 4 weeks after surgery or with a minimal inter-treatment interval of 4 weeks for previously treated patients.

Results: 29 Patients were treated, with a median age of 51 years. FIGO stages III and IV were present in 76%. 25 Patients had prior surgery, 5 had prior chemotherapy. 22 Patients completed 6 cycles. Treatment was prematurely stopped because of hypersensitivity reactions (8%), progressive disease, or nephrotoxicity. No grade IV toxicity was seen. Grade III toxicity consisted of anemia (19%), leucopenia (21%), thrombocytopenia (19%), nausea/vomiting (10%), and neurotoxicity (8%).

21 out of 26 patients had a normalisation of the CA-125 within 4 cycles of TGC. The response rate was 84%, with 65% complete responses. Stable disease was present in 8% (one with recurrent disease). Progressive disease was present in 2 patients (8%), one with recurrent disease. Median response duration was equal or more than 11 months. Overall survival was equal or more than 14 months.

Conclusion: The combination of paclitaxel, gemcitabine, and cisplatin is feasible and active in the treatment of advanced ovarian cancer, both in primary as in recurrent disease.

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Experience with topotecan as salvage therapy for epithelial ovarian cancer in a cancer centre

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Background: Relapsed ovarian cancer is an incurable disease, with a particularly poor prognosis for those who relapse within 6 months of first-line treatment. Clinical trials have demonstrated that topotecan is one of the most active drugs in this setting, but is associated with significant haematological toxicity in 70-80% of those receiving it at standard doses. We performed a retrospective audit of patients receiving off-study topotecan at the Beatson Oncology Centre, Glasgow to assess response and toxicity using WHO criteria.

Methods: Between 1998 and 2000, 41 patients received topotecan at our centre. Clinical or radiological response data were available for 36 patients and Ca125 response data were available for 34 patients. Median age was 55 (39-73), and median number of cycles delivered was 3 (1-6). Dosing and scheduling varied from 0.75mg/m2 -1.5mg/m2 for 3, 4 or 5 days. Ninety-seven and 89% of patients had received prior platinum and prior taxane therapy, respectively. Fifty one percent of patients were platinum refractory and 54% taxane refractory, as judged by progression on therapy or relapse within 6 months of treatment.

Results: Overall clinical response rate was 11%, with a Ca125 response rate of 35%. A further 9 patients (21%) had stable disease. All 4 patients responding to treatment (2CR and 2PR) had received 1.5mg/m2 of topotecan (3 patients received treatment over days 1-4, 1 patient over days 1-5). Of the clinical responses seen, 3 (2 CR and 1 PR) were in patients neither platinum nor taxane refractory. Only one response (PR) was observed in a

patient refractory to either platinum or taxane. Grade 4 neutropenia occurred in 48% and febrile neutropenia in 17%. Two septic deaths occurred during treatment (1 patient receiving 1.25mg/m2 over 5 days, 1 patient receiving 1.5mg/m2 over 5 days). Twenty seven percent (11) patients experienced dose delays (7of whom received 1.5mg/m2 dose) and 17% (7 patients) had a dose reduction (4 of whom received 1.5mg/m2).

Conclusions: The response rate is lower than was anticipated and is likely to be a function of dose delays and reductions, and the high frequency of platinum and/or taxane-refractory disease. Our data suggest that the optimal use of topotecan in the off study salvage setting is in minimally pre-treated, fit patients at a dose level of 1.5mg/m2 over 4 or 5 days. Randomised studies comparing topotecan with less toxic alternative therapies (such as oral VP16) in this setting are warranted.

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Efficacy and toxicity of chemotherapy (Carboplatin/Ifosfamide) combined with whole body hyperthermia (WBH) in patients with recurrent ovarian cancer - a phase II study (dolphin-1-study)

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Purpose: Despite several improvements in the cytostatic treatment over the last years, the prognosis of patients with recurrent ovarian cancer still remains unfavorable. There is some evidence that the combination of whole body hyperthermia (WBH) with special cytostatic agents (e.g. carboplatin, ifosfamide) leads to a higher efficacy through increased cellular metabolism and immunostimulation.

Methods: In an ongoing prospective multicenter phase II Study we are evaluating the toxicity and efficacy of 11 patients (38 treatment courses) with recurrence of ovarian cancer receiving WBH (target temperature 41.8°Celcius over 1 hour) combined with carboplatin AUC5 and ifosfamide 3g/m2 every 28 days, for 6 cycles or until progression. Patients (=65 years) are required to have sufficient cardiac, pulmonal and renal function.

Results: Toxicity lead to dose reduction in 14 courses (36,8%). The following toxicities (NCI) were seen: myelotoxic side effects as grade 3 leucocytopenia in 11 cases (28,9%) and grade 4 leucocytopenia in 6 cases (15,8%). Thrombocytopenia grade 3 occurred in 9 courses (23,7%), grade 4 in 7 courses (18,4%). In 2 courses renal toxicity grade 2 appeared. In 10 courses (26,3%) skin burnings grade 2 and in 4 courses (10,5%) skin burnings grade 3 were reported. No other severe treatment related adverse events were noted. Preliminary data on efficacy include 5 patients with partial remission, 4 patients with stable disease and 1 patient with progression.

Conclusion: The combination of carboplatin and ifosfamide with WBH is well tolerated and appears to be feasible and safe. After the successful completion of the phase II sequence (15 patients) the study will continue as a randomised multicenter phase III study, comparing above treatment with normothermic cytostatic application. This will be the first phase III trial to evaluate the efficacy of WBH combined with chemotherapy.

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Chemotherapy with carboplatin/docetaxel for primary and recurrent epithelial ovarian cancer

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The high incidence of peripheral neurotoxicity associated with platinum/paclitaxelcontaining chemotherapy for ovarian carcinoma is frequently a limiting factor with respect to long term treatment. A pilot study was conducted with docetaxel instead of paclitaxel to investigate if incidence of neurologic toxicities could be decreased withoutcompromising tumor response.

Sixty-one pts with epithelial ovarian cancer (FIGO II-IV), were treated with the combination of carboplatin (AUC 5) and docetaxel (75mg/m2), i.v., q3w. Twenty-nine pts received 6 courses of carboplatin/docetaxel as first-line treatment for ovarian carcinoma. A further 32 pts were treated with carboplatin/docetaxel for relapse >12 months as second line therapy.

A total of 300 courses was administered: Predominant WHO grade 3/4 toxicity was leucopenia (21/61). Grade 3 thrombocytopenia occurred in 5% of pts. No Grade 3 neuropathy was observed,. Grades 2 and 1 neuropathy was seen, respectively, in only 2/61 pts and 16/61 pts. In the second-line cohort, neurotoxicity was not increased. 12/61 pts complained of mild to moderate fluid retention, mild to moderate nausea and vomiting (WHO 2/3) occurred in 24/61 pts. No ototoxicity was observed.

Of 26 first-line patients evaluable for response, ORR (CR + PR) was 79%. Thirty second-line pts were evaluable for responsewith ORR of 75%. Calculated median TTP for first-(23/29) and second-line cohorts (23/32) was 10 and9,4 mos, respectively.

In summary, the observed efficacy of carboplatin/docetaxel combination therapy for ovarian carcinoma is comparable to that reported for platinum/taxane combinations. Nevertheless toxicities, particularly neurologic side effects are less severe and less predominant with carboplatin/docetaxel.

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Complement activation in ovarian cancer

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Background: Activation of the complement system plays a key role in the inflammation process and in protecting the host from pathogenic agents, e.g. viruses and bacteria. Complement activation has also been observed in connection with neoplastic disease. The aim of the present study was to determine whether complement is activated in patients with cystic ovarian tumors and if the degree of activation differs in malignant and benign tumors.

Methods: C4d, Factor Bb, C3a/C3a-desArginine and SC5b-9 were measured in 65 patients with lower abdominal cystic ovarian tumors, including 31 ovarian cancers and 35 benign ovarian tumors. Patient age and tumor size did not differ significantly between the two groups. The levels of C4d, Factor Bb and SC5b-9 were determined in plasma, in ascites and in cyst fluid with Enzyme Immune Assay (EIA) methods. Levels of C3a/C3a-desArginine were determined in the same compartments with an ELISA procedure.

Results: C4d and C3a/C3a-desArginine were significantly elevated in plasma, ascites and in cyst fluid in patients with malignant ovarian tumors compared to patients with benign tumors. Factor Bb and SC5b-9 showed significantly higher levels in plasma and in cyst fluid in patients with malignant cystic ovarian tumors compared to those with benign tumors.

Conclusions: This study shows that complement is activated in patients with ovarian cystic tumors. There is a significantly higher grade of activation in patients with malign ovarian tumors than in patients with benign cystic tumors in the ovaries.

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Long-term survival with consolidation intraperitoneal chemotherapy (IP) in advanced ovarian cancer (AOC) with complete pathological remission

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Intraperitoneal (IP) chemotherapy (CT) in AOC demonstrated significant activity in patients with small-volume residual disease (RD), as part of the initial chemotherapy or after failure of IV CT. However, long term evaluation is seldom reported. We report our results with consolidation IP CT in patients who achieved a complete pathological response after IV CT. This study included patients (pts) with AOC (stage III-IV, under 70 yrs) who entered in four prospective trials (1984-1997) including IV CT based on cisplatin (6 cycles) and anthracyclines, early debulking surgery after three cycles of CT in case of initial RD over 2 cm, second-look laparotomy (SLL) and intraperitoneal consolidation CT (Proc ASCO; 10:639, 1991; Proc ASCO; 12:888, 1993; Eur J Cancer; 28:53, 1992). Among 219 pts, 68 with biopsy negative second-look laparotomy received every 4 weeks 3 consolidation cycles of IP CT via a totally implantable port. Fifty six patients received mitoxantrone 25 mg/m2 D 1, VP16 120 mg/m2 D 1. In 16 pts, IP cisplatin 100 mg/m* was added (no previous neuropathy). Nine patients received high dose cisplatin (200 mg/m*) and 3 patients had cisplatin 200 mg/m*+cytarabine 2g. Only 13 pts (19%) did not receive the full 3 cycles.