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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