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## PREGNANCY AFTER SUCCESSFUL TREATMENT OF GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

*M. Malek, H. Raïs, A. Houidi, M. El May, H. Chelli, F. Ben Ayed*
*Institut Salah Azaiz (ISA), Tunis, Tunisie*

Although GTD is uncommon, it is extremely important because of the high degree of curability with adapted treatment. It is becoming important to preserve young patients (pts) fertility. We reviewed the productive history of all pts who received chemotherapy (CT) for a GTD at ISA, between January 1982 and December 1993. Only 34 pts had subsequent pregnancies: 19 had molar pregnancies (MP) and 15 choriocarcinomas (CC). The mean age was 27 years (range 17–38). Pts with CC received a combined regimen of CT with Vincristin and Methotrexate 9 pts and Etoposide and Actinomycin 6 pts. All those with MP were treated by a CT associating (Methotrexate and Vincristin). All of them entered a complete remission, 7 after a salvage CT.

| | MP n = 15 | CC n = 19 |
|---|---|---|
| Number of pregnancies | 28 | 29 |
| Normal term pregnancies | 18 | 23 |
| Spontaneous abortion | 3 | 1 |
| Ectopic pregnancy | 0 | 1 |
| Placenta Acreta | 0 | 0 |
| Premature birth | 1 | 1 |
| Congenital malformations | 3 | 3 |

*Conclusion:* It is actually important to achieve 2 objectives in treating pts with GTD: first to cure them, second to preserve their fertility.

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## A PHASE I STUDY OF PACLITAXEL (TAXOL®)(TXL) AND CARBOPLATIN (CBDCA) IN THE TREATMENT OF ADVANCED OVARIAN CANCER

*C. Zamagni, A. Martoni, N. Cacciari, F. Pannuti*
*Medical Oncology Div. S. Orsola-Malpighi Hosp. Bologna, Italy*

An open non-randomized dose finding pilot study was started to evaluate the MTD and the efficacy of the combination TXL-CBDCA. Previously chemotherapy untreated patients with stage III and IV ovarian cancer are eligible for the study. Three patients are required at each dose level and standard criteria are employed to define MTD. TXL is administered as 3-hour iv infusion, followed by CBDCA 30 minutes iv infusion. Premedication with corticosteroids and antihistamines is required. The first dose level was TXL 125 mg/m$^2$ and CBDCA 250 mg/m$^2$: the dose level progression is done by firstly increasing TXL (25 mg/m$^2$) and then CDBCA (50 mg/m$^2$). Up to now 9 pts entered the study and the 3rd dose level (TXL 150 mg/m$^2$; CBDCA 300 mg/m$^2$) has been completed, without reaching the MTD. Twenty-six courses have been administered (15 level I; 7 level II and 4 level III). Gr. 4 toxicities were not observed; gr. 3 alopecia occurred in all pts; gr. 3 neutropenia occurred in 36%, 20% and 50% of courses at dose level I, II and III respectively. No thrombocytopenia occurred. Gr. 2 vomiting was observed in 30% of courses. Advanced results of this study are planned to be available for ECCO 8 meeting.

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## PACLITAXEL ± IFOSFAMIDE IN ADVANCED OVARIAN CANCER (A.O.C.). PRELIMINARY RESULTS OF A MULTICENTRIC PILOT STUDY

*L. Miglietta, D. Amoroso, M. Bruzzone, C. Granetto, E. Catsafados, S. Mammoliti[1], D. Guarneri, F. Pedullà[2], G. Foglia[2], N. Ragni[2], F. Boccardo*
*Ist. Naz. Ricerca sul Cancro*
*[1]Galliera Hospital*
*[2]Department of Obstetrics and Gynecology, Univ. of Genova, Italy*

Paclitaxel activity with or without ifosfamide was investigated as salvage therapy in patients (pts) with a.o.c. Group I (n = 20 evaluable) pts received taxol alone 175 mg/m$^2$, over 3 hours, every 3 weeks. Group II (n = 13 evaluable pts) received taxol 135 mg/m$^2$ as in Group I; escalating doses of ifosfamide (1; 1.5; 2 gr/m$^2$) was administered on days 2–3 with mesna rescue. In absence of severe toxicity, ifosfamide was administered at 2 gr/m$^2$ for the last three cycles. The average number of courses was respectively 4 in Group I (range 1–8) and 3 in Group II (range 1–6). Overall, 3 PR were observed in 15 pts with primary platinum resistant disease, 2 PR were observed in 8 pts with platinum sensitive disease while no response was observed in 10 pts with secondary platinum resistant ovarian cancer. Our results, although preliminary, suggest that taxol ± ifosfamide show a moderate but definite activity in so heavily pretreated category of pts. As expected the activity in platinum sensitive pts was twofold the activity achieved in platinum resistant pts, showing respectively 25% of PR vs 12% of PR. However, was to note that a 20% of activity was observed in primary platinum resistant pts. Moreover taxol plus ifosfamide association seems not to achieve better results than taxol alone, while it showed a higher haematologic toxicity. It is concluded that the number of previous therapeutic lines rather than the intrinsic sensitivity to cisplatin front line treatment is probably the major determinant of taxol activity when employed as salvage treatment.

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## TAXOL (TAX) AND ESCALATING DOSES OF IFOSFAMIDE (IFO) IN ADVANCED BREAST AND OVARIAN CANCER PATIENTS (PTS)

*A. Romanini, P.G. Giannessi, M. Conti, M. Da Prato, A. Tognoni, A. Gadducci, A. Fanucchi, P.F. Conte*
*Medical Oncology, Santa Chiara Hospital, Pisa, Italy*

TAX and IFO are active drugs in antracycline and cisplatin (Pt) resistant breast and ovarian cancer. The objective of this study was to assess the MTD of IFO given in a 3-day c.i. preceded by a fixed dose of TAX (175 mg/m$^2$) in a day hospital setting. Thirteen women with ovarian (9) and breast (4) cancer with advanced disease, pretreated with two or more chemotherapy regimens entered this study. Median age was 57 (range 33–69). All pts had previously received epidoxorubicin at a median dose of 360 mg/m$^2$ (range 360–1260) alone or in combination with Pt or 5-fluorouracil and cyclophosphamide. All pts received a 3-hour infusion of a fixed dose of TAX through a central venous infuse port, followed by a 3-day c.i. of escalating doses of IFO (4-5-6-7 g/m$^2$) and equal doses of Mesna, every 21 days in subsequent groups of pts. G-CSF was given only for G4 neutropenia (N) lasting longer than 72 h or febrile G4 N. MTD was defined as follows: any G4 N lasting longer than 7 days or neutrophyls <100/mL for more than 72 h despite G-CSF, any G4 febrile N for more than 72 h, any G4 thrombocytopenia, any G3 non-hematologic toxicity, except for alopecia. Hematologic toxicity and related events were:

| | IFO dose level (g/m$^2$) | | |
|---|---|---|---|
| | 4 | 5 | 6 |
| no. of pts/no. of courses | 6/32 | 6/17 | 2/2 |
| median courses/pts (range) | 5.5 (1–8) | 2 (1–5) | 1 |
| leukopenia WHO G3/4 (% of courses) | 16 (50) | 7 (41) | ne |
| neutropenia WHO G3/4 (% of courses) | 16 (50) | 11 (65) | ne |
| anemia WHO G3 (% of courses) | 1 (3) | 4 (24) | ne |
| fever >38°C (% of courses) | 1 (3) | 3 (18) | ne |
| G-CSF vials/pts (% of courses) | 14 (10) | 35 (35) | ne |
| red cells transfusion (% of courses) | 0 (0) | 4 (24) | ne |

No other non-hematologic toxicity except alopecia was seen.

Responses are as follows: 2 CR, 1 PR, 1 SD, 1 PD, 1 NE, among the pts treated at the first dose level; 1SD and 5 too early, at the second dose level. The MTD has not yet been reached, but the combination TAX + IFO has acceptable toxicity and activity.

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## TRIAL OF ORAL HEXALEN FOR RELAPSED OVARIAN CARCINOMA [OV/CA]: COMPARISON OF CA125 AND EORTC RESPONSE DEFINITIONS

*G.J.S. Rustin[1,2], S.M. Crawford[3], R.E. Coleman[4], J. Lambert[5], J.A. Ledermann[6], M. Soukop[7], S. Karp[8], R.H. Phillips[1], N. Habboubi[9], K. Meely[9]*
*[1]Middlesex & Charing Cross [2]Mount Vernon, [3]Airedale, [4]Western Park, [5]Hammersmith, [6]UCH & Middlesex, [7]Glasgow RI, and [8]Nth Middlesex Hospitals,*
*[9]USB Pharma, U.K.*

Between 11/91 and 11/94 71 patients (pt) with recurrent ov ca were entered into a trial of oral Hexalen 260 mg/m$^2$ in divided doses daily for 14 days per month [mo]. Eligibility criteria included a treatment free interval of >6 mo, complete clinical remission and serum CA125 <35 u/ml with initial & up to one 2nd line chemotherapy. Response was evaluated according to EORTC criteria in 38 of the 57 eligible pts. PR was assessed according to CA125 in 45 pts & was predicted if after 2 samples there was a ≥50% fall confirmed by a 4th sample, or a serial fall over 3 samples >75% (Rustin G, Ann Oncol suppl 4, 71–77:1993). Toxicity was assessed according to NCI criteria & is available on 65 pts. 13 pts were withdrawn because of toxicity which was mainly nausea [G 2 or 3 in 25), vomiting [G 2 or 3 in 18] and tiredness [G 2 or 3 in 17].

With increasing experience it was found that a combination of domperidone, dexamethasone & chlorpromazine at night controlled this toxicity in most pts. G 2 anaemia but not G 3 or 4 was seen in 5, G 2 or 3 neutropenia in 2 and G 1 & 3 thrombocytopenia in 2 pts. G 1 neurotoxicity was seen in 5 and G 2 in 6. Median treatment free interval was 12 mo. Responses [CR + PR] were seen in 15 (39%) [95% CI 24–55] of those evaluated according to EORTC & in 16 [36%] [95% CI 21–50] of those evaluated according to CA125. Overall response rate was 22 of 53 [42%] & was related to treatment free interval, 6 to 12 mo 32%, >12 to 24 mo 60% and >24 mo 57%. Median duration of response was 8 mo. Oral Hexalen is a highly efficient & well tolerated agent in pts relapsing after previously responsive ov ca. Response evaluation by a strict CA125 definition gives similar conclusions regarding efficacy of Hexalen to the EORTC criteria.

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## H-CAP REGIMEN RESULTS IN LONG TERM SURVIVAL IN OVARIAN CANCER

*H. Jones, J.D. Hainesworth, B.J. Scheffler, F.A. Greco*
*Vanderbilt Univ Medical Center North, Nashville, TN, U.S.A.*

Clinical trials of Hexalen® (altretamine, hexamethylmelamine) in combination with cyclophosphamide, doxorubicin and cisplatin (H-CAP) as first line therapy for patients with advanced ovarian cancer were conducted at Vanderbilt University. Patients received 6 monthly courses of Hexalen (H), 150 mg/m$^2$ po days 1 to 14, cyclophosphamide (C) 300 mg/m$^2$ iv days 1 and 8, doxorubicin (A) 20 mg/m$^2$ iv days 1 and 8 and cisplatin (P) 60 mg/m$^2$ iv day 1. The survival data from this cohort of 55 patients were compared with those of a subsequent cohort of 22 patients treated with the identical dose and schedule of C, A and P. Results demonstrate a statistically significant survival benefit for H-CAP relative to CAP despite poorer prognostic characteristics: 36% of H-CAP patients had ≤3 cm residual disease vs 86% of CAP patients. Median survival for H-CAP patients was 45 months vs 29 months for CAP patients ($P$ = 0.006). For patients with <3 cm residual disease, median survivals were 101 months for H-CAP vs 32 months for CAP; 45% of these H-CAP patients are alive at 9 years vs 10% of these CAP patients ($P$ = 0.003). The addition of Hexalen to CAP resulted in significantly improved survival but no increase in toxicity. Hexalen warrants further evaluation as part of first line combination regimens for advanced ovarian cancer.

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## PHASE II STUDY OF CISPLATIN (P), VINBLASTINE (V) AND BLEOMYCIN (B) IN RECURRENT OR ADVANCED DYSGERMINOMA (D)

*A.T. van Oosterom, G. Favalli, A. Kobieska, A. Pawinsky, T. Sahmoud, S. Pecorelli*
*EORTC Gynecological Cancer Group*

Dysgerminomas account for 1% of all ovarian cancers and 50% of all ovarian germcell malignancies. Half of the pts can be cured with local treatment. Eighteen pts with advanced D were entered in this study. Age 27 (range 13–48) yrs. Seventeen had prior surgery, one prior radiotherapy (RT). Delay since initial diagnosis was median 11 weeks. PS 12:0, 3:1, 3:2. Three had only a local recurrence; all others also metastatic disease. Treatment consisted of P 20 mg/m$^2$ d 1–5, V 0.15 mg/kg d 1,2, B 30 mg d 2,9 and 16 q 3 wks. Twelve pts obtained a CR (66%), five a PR (27%) and one could not be evaluated since immediate RT followed the CT. Of 18 pts 14 are alive and well, four died: 2 of progressive disease, 2 toxic death (one of septicaemia in leucopenia and one of lung fibrosis). Eighteen pts had 4 cycles, one 3, one 5 and one 6. Toxicity was as usual for this regimen: gr 3–4 leucopenia 78%, thrombocytopenia 17%, N&V 33% and alopecia.

*Conclusion:* PVB is a very active regimen in adv. D. with an overall RR of 93% and a 77% rel. free survival after 3$^+$ yrs.

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## RHIL-3 AND G-CSF VS G-CSF ALONE AFTER TAXOL-IFOSFAMIDE-CISPLATIN (TIC) CHEMOTHERAPY (CT) IN RESIDUAL/PROGRESSIVE OVARIAN CANCER (OC)

*G.J. Veldhuis, P.H.B. Willemse, W.T.A. van der Graaf, J.G. Aalders[1], A. Groenewegen[2], E.G.E. de Vries*
*Department of Med Oncol & of Gynecol*
*Univ. Hosp Groningen, The Netherlands*
*[2] Sandoz BV, Uden, The Netherlands*

Treatment of residual or progressive OC after 1$st$-line CT remains unsatisfactory. A study was designed to test a new CT-regimen for this group of pts, furthermore, bone marrow protecting properties of a combination of rhIL-3/G-CSF vs G-CSF alone were evaluated. CT consisted of iv TIC chemotherapy (T: 135 mg/m$^2$ d1, I 1200 mg/m$^2$/d, d2–4 and C 30 mg/m$^2$/d, d2–4), in cycles without grade IV hematological toxicity taxol dose escalation was performed. Pts were randomized to arm A: rhIL-3 (10 μg/kg/d sc, d5–9) and G-CSF (5 μg/kg/d sc, d7–16) or arm B: G-CSF (as in A) alone. Four cycles (q21d) were scheduled. Until now 14/16 pts are evaluable for toxicity and efficacy. Nausea, vomiting and malaise were frequently observed in both arms, flu-like symptoms in 6/8 pts (A) vs 1/6 (B). Reversible peripheral neuropathy between cycles was reported in 4/8 pts (A) vs 3/6 (B), long-lasting peripheral neuropathy in 3/8 pts (A) vs 0/6 in (B). One pt (A) developed venous thrombosis, which reoccurred after rhIL-3. One pt (B) was hospitalized for bleeding in liver metastases. 65% of the cycles were 3-weekly (A) vs 50 (B). Grade IV neutropenia occurred in 27% of the cycles (A) vs 13 (B). Grade IV thrombocytopenia was observed in 50% of the cycles (A) vs 13 (B, $P$ = 0.03). Platelet recovery tended to be faster in arm A. Tumor responses were achieved in 4/8 pts (A) vs 4/6 (B), a 57% overall response rate. TIC offers a promising regimen in residual and progressive OC after 1$st$-line CT. Synergistic effects of rhIL-3/G-CSF were limited with regard to platelet nadir, but platelet recovery was faster.

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## CLINICAL (WHO) AND SERUM TUMOR MARKER (CA125) RESPONSE TO PLATINUM BASED CHEMOTHERAPY AFTER TREATMENT WITH PACLITAXEL IN PATIENTS WITH OVARIAN CANCER (OVCA)

*J.B. Vermorken, R.V.H.P. Huijskes, K. Hoekman, C.W. Burger, R.H.M. Verheijen, M.A. Heitbrink, H.M. Pinedo*
*Departments of Medical Oncology, Gynecologic Oncology and Radiology, Free University Hospital, Amsterdam, The Netherlands*

*Background:* At present, 60% to 90% of the patients (pts) with OVCA demonstrate objective responses to first-line platinum (Pt)-based combination chemotherapy (CT). Serial CA 125 measurements reflect the clinical course of the disease in these circumstances correctly in 89% of the cases (Neth J Med 40:36, 1992). In pts treated with paclitaxel (Taxol®, T) after Pt-based CT this correlation is poor (Proc ECCO-VII; 133, 1993). The question can be raised whether this poor correlation is a general phenomenon in relapsed OVCA pts or whether this is related to the use of T.

*Objectives:* to determine clinical response and CA 125 response with Pt-based CT after T treatment and to assess the correlation of serum CA 125 levels with the clinical course with both treatments, i.e. with T and with Pt-based CT after T.

*Methods:* Doubling or halving of CA 125 levels were considered to be a significant increase or decrease. For the relationship with the clinical course we used the Spearman rank correlation.

*Results:* So far, 18 pts (with 6/18 clinical responses and 15/16 marker responses on T) were pre-treated with a Pt-based CT, 9 in 3rd-line, 6 in 4th-line, and 3 in 5th-line. 7 Pts responded (39%; 2 CR, 5 PR) according to WHO criteria and 8 of 15 evaluable pts (53%) had a CA 125 response. The correlation between changes in CA 125 levels and clinical course was poor for T (correlation 0.27; $P$ = 0.31), but significant for Pt-based CT (correlation 0.67; $P$ = 0.0066).

*Conclusions:* 1) Pt-compounds and T are not cross resistant 2) the poor correlation between changes in serum CA 125 levels and the clinical course of the disease seems to be specific for treatment with T.