Gynaecological cancers I

525 ORAL

Response and early progression according to CA 125 to assess activity of topotecan vs paclitaxel in relapsed ovarian carcinoma

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Purpose: We have shown that response of ovarian cancer can be defined by a serial fall of CA 125 *[J. Clin Oncol 1996,* **14:** *1545–51].* To help rank the activity of drugs we have now compared both response and progression rate according to CA 125 in the SmithKline Beecham trial of paclitaxel (P) versus topotecan (T) for first relapse. Because CA 125 may over estimate response to taxanes, we tested both CA 125 response and progression definitions.

Methods: 112 patients (pts) received T 1.5 mg/m^2 d x 5 and 114 received P 175 mg/m^2 as a 3 hr infusion, both q 21d. Response was assessed by EORTC criteria (EC) in 204 pts, by CA 125 in 165, and CA 125 progression was assessed in 180. CA 125 progression was based on a 25% increase over 4 samples or 50% increase over 3 samples or persistence of >100 U/ml for >2 months (m) calculated by a computer programme *[Ann Oncol 1994,* **4:***S71–77].*

Results:

	Clinical response	CA 125 response	Clinical progression	CA 125 progression
Topotecan	24%	20%	53%	21.9% (CI 13.6–32.5)
Paclitaxel	14%	21%	63%	35.7% (CI 26.3–46.0)

Both drugs were active according to CA 125 response. However there was a higher early progression rate by 4 months in those receiving P versus T by both clinical (p = 0.12) and CA 125 criteria (p = 0.04).

Conclusion: In trials of new drugs for ovarian carcinoma the use of CA 125 response and progression criteria may be helpful in deciding whether further development of a drug is justified.

526 ORAL

Outome of advanced epithelial ovarian cancer in women under 40 years

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Purpose: We have studied the outcome of treatment of epithelial ovarian cancer (EOC) in women under 40 years treated in three randomised phase III studies of platinum-based chemotherapy between 1984 and 1994.

Methods: 652 patients (pts) were entered into trials of carboplatin versus carboplatin plus radiotherapy, carboplatin v. iproplatin, and carbo- or cisplatin (5 v. 8 cycles). 28 were excluded on histological review with non invasive EOC.

Results: Median age of 624 pts was 60 yr (17–79). 29 (4.6%) were under 40 yr. FIGO stage, grade and residual disease were significantly worse in pts >40 yr. but histology and performance status (ECOG) were not different. Response was assessed by second look laparotomy in 229 patients (9 under 40 yr) and by CT scans and/or serum CA125 in the others. The median follow up is 5.2 yr. Survival and time to progression were significantly better in women under 40 yr. At 5 yrs, for those under and over 40 yr the RFS is 58.6% and 16% (95% CI: 24.3–60.8%) p < 0.0001 and the OS is 65.2% and 20.1% (95% CI: 27.2–63%) p < 0.001. No pts <40 yr relapsed after 1.5 yr. A Cox proportional hazards model identifed age <40 yr as a good prognostic variable for serious histology (hazard ratio (hr): 2.1). Other prognostic factors were ECOG (hr: 1.3), residual disease (hr: 1.3), and stage (hr: 1.4).

Conclusions: The biology of serous carcinomas of the ovary in young women appears to be different from older women and is associated with a more favourable outcome.

527 ORAL

Immunotherapy of advanced ovarian cancer with the anti-idiotypic antibody MAb ACA 125 – Results of a clinical phase IB study

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Purpose: The idiotypic network offers a method for immunotherapy by presentation of tumor antigens as an idiotypic determinant in a different environment. Therefore, we have generated an IgG1 murine monoclonal anti-idiotype antibody (Ab2) designated ACA 125, which mimics a specific epitope on the tumor-associated antigen CA 125. We used ACA 125 as a surrogate for the tumor-associated antigen CA 125 for vaccine therapy.

Methods: 18 patients with advanced epithelial ovarian cancer (n = 5) or recurrences (n = 13) received a minimum of three injections up to nineteen injections of the complete anti-idiotype MAb ACA125 at a dosage of 2 mg per injection.

Results: 11 of 18 patients developed anti-anti-idiotypic (Ab3) responses to the ACA 125. 9 of 18 patients developed a CA 125 specific cellular immune response by their PBL. The median progression free survival in those patients, who showed a specific immune response to the tumor-associated antigen CA 125, was 10.3 months without any other therapy, in contrast to 7.1 months in the anti-anti-idiotype negative group.

Conclusion: This is the first clinical trial of the induction of a specific active immunity to the tumor-associated antigen CA 125 in patients with advanced ovarian cancer treated with an anti-idiotype antibody that "mimics" CA 125. Patients showed the development of a specific humoral and cellular immune response to an otherwise non-immunogenic tumor antigen. (supported by DFC, Wa 740/1–3).

528 ORAL

A phase II study with GI147211 in ovarian cancer

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GI147211 is a water soluble analog of camptothecin with preclinical antitumor activity in a broad range of tumor xenografts. Main toxicities reported in Phase I studies were hematologic and gastrointestinal.

The ECSG has performed a Phase II study in ovarian cancer at the recommended dose of 1.2 mg/m^2/dx5 q3wks. Patients (pts) were stratified for "response to prior treatment". O_1 were pts relapsing/progressing during or <4 months after last platinum (Pt)-containing treatment; O_2 were pts relapsing between 4–12 months after the last Pt-containing regimen. Pts could have had 2 prior Pt regimens. A total of 55 eligible pts were entered (27 O_1, 28 O_2) of whom currently 23 O_1 and 23 O_2 are evaluable for response. 208 (median 4, range 1–12) cycles (c) were administered, with dose reductions to 0.9 mg/m^2/d in 51 c and to 0.6 mg/m^2/d in 2 c, mostly due to hematologic toxicity. Dose escalation to 1.5 mg/m^2/d was possible in 11 c. Main hematologic toxicities were neutropenia (grade 3/4 in 21%) and anemia (grade 3 in 9%). Asthenia, nausea, and alopecia were the main non-hematologic toxicities, but rarely exceeded grade 2. 1/23 O_2 pts developed a CR and 7 pts (3/23 O_1, 4/23 O_2) had a PR.

We conclude that GI147211 has moderate activity in Pt-pretreated ovarian cancer.

529 ORAL

Weekly high dose cisplatin (P) and daily oral vepesid (VP): A highly active salvage regimen for progressive or recurrent ovarian cancer after platinum therapy

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Purpose: To increase the efficacy of P in ovarian cancer by weekly administration.

Methods: 92 Patients (pts) were treated with 2 cycles of weekly P day 1, 8, 15 and daily oral VP 50 mg, day 1–15 q. day 29, followed by VP 50 mg/m^2/day, day 1–21 q day 29, times 9. The P dose for pts with a P free interval (PFI) of <1 year was 70 mg/m^2 and for a PFI of >1 year 50 mg/m^2.

All pts had received prior treatment with platinum containing combination chemotherapy.

Results: The median P dose/week received for P70 (57 pts) was 42 (24–52.5) mg/m²/wk, for P50 (35 pts) it was 32 (20.6–37.5) mg/m²/wk. The WBC nadirs were median 1 85 (0.64–8.9) × 10^9/l and 2 1 (0.75–4.9) × 10^9/l and the Plts nadirs were median 67 (8–193) × 10^9/l and 127 (11–320) × 10^9/l, respectively. 5 P70 pts had nephrotoxicity grade 2. Neurotoxicity grade 2 was observed in 4 P70 pts and 3 P50 pts. The response rate according to the PFI is shown in the table.

Response	PFI < 3 m N = 22	PFI 3–6 m N = 14	PFI 6–12 m N = 21	PFI > 12 m N = 35
CR	18%	22%	33%	57%
PR	18%	57%	62%	34%
Overall RR	36%	79%	95%	91%

The response duration for the patients with a PFI of <1 year was median 10 m, range (4–29⁺)m and for pts with a PFI ot of >1 year median 14 m, range (3.5–29⁺)m.

Conclusion: Salvage therapy with weekly cisplatin and oral vepesid is highly active Combination chemotherapy with weekly cisplatin should be tested in first-line.

530 ORAL

Efficacy of a combination of irinotecan (CPT-11) with mitomycin-C (MMC) for clear cell carcinoma of the ovary (OCCA) which is intrinsically platinum-resistant

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Purpose: To assess the efficacy of a combination of CPT-11 with MMC for OCCA which is intrinsically platinum-refractory.

Methods: Eligible patients (pts) had histologically-confirmed pure OCCA progressed during platinum-based chemotherapy (CTX) or relapsed within 6 months after the end of this CTX, measurable lesions, WHO PS ≤ 3, age ≤75, adequate hematopoietic, liver and renal functions, and written informed consent.

Protocol: CPT-11 (140 mg/m², IV infused over 4 hours on day 1, 15, and 29) and MMC (7 mg/m², IP injection through a reservoir on day 1, 15, and 29). The course was repeated every 3 weeks.

Results: To date 24 pts with OCCA were entered, of whom 7 had failed to respond to prior CPT-11 alone subsequent to platinum-based CTX. The median age was 53 (40–69). Among total 73 courses, grade 3 diarrhea was observed in 8 courses. Other toxic signs were acceptable. The responses by tumor size were 2 CR, 2 PR, and 1 NC for ≤2 cm in diameter, and 2 CR, 5 PR, 9 NC, and 3 PD for >2 cm. Eleven responders have showed a significantly longer survival compared with 13 non-responders (median survival after the start of CTX: 21 months vs 8 months, p < 0.001 for Log-rank test).

Conclusion: CPT-11 plus MMC was the first regimen to demonstrate a significant activity with survival benefit for intrinsically platinum-resistant OCCA. Further studies with this regimen are warranted in previously untreated pts with OCCA.

531 ORAL

Cisplatin/paclitaxel vs carboplatin/paclitaxel: Optimizing of treatment in advanced ovarian cancer

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Purpose: Recently, it has become evident that in advanced ovarian cancer primary chemotherapy with Paclitaxel/Cisplatin is more effective than the combination Cyclophosphamide/Cisplatin. An issue that has to be addressed is to decrease the severity of side effects by substituting the nonneurotoxic analogue carboplatin for cisplatin.

Methods: Patients FIGO stage IIb–IV were randomised to two treatment arms receiving either Paclitaxel 185 mg/m² plus Carboplatin AUC = 6 mg/ml/min (Arm A) or Paclitaxel 185 mg/m² plus Cisplatin 75 mg/m² (Arm B). 6 cycles were administered every 3 weeks. Patients followed stratification of <1 cm vs. >1 cm residual tumor.

Results: After 12 months 382 patients were enrolled in the ongoing study protocol Hematological toxicity occurred more frequently in Arm A, febrile neutropenie > grade 2 was not observed. G-CSF, antibiotics or red blood cells were given in less than 4% of courses in both arms. Treatment delay ≥7 d was observed in 13% and 7% in Arm A and Arm B, dose reduction was necessary in less than 5% of courses in both arms. Grade II neuropathy occurred in 17% and 33% of pts. in Arm A and Arm B, respectively.

Conclusion: Accrual is still going on. Except for alopecia, non-hematological toxicity occurred more frequently in Arm B.

532 ORAL

Long term survivors from a European-Canadian trial of paclitaxel in platinum-pretreated ovarian cancer (OVCA)

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In a randomized European-Canadian study, 2nd or 3rd line paclitaxel (P) was given to 391 pts with recurrent OVCA. Results of the trial comparing two doses and schedules of P have been reported (JCO 12: 2654, 1994). Long term data indicate 65 pts lived >2 yrs after receiving P. In order to determine if pt characteristics at study entry were related to likelihood of long survival (LTS), both groups were compared with respect to 23 baseline variables Univariate results are shown:

	>2 yr survivors (n = 65)	<2 yr survivors (n = 326)	p value
Mean age (yrs)	53.1	56.7	0.018
Performance status 0	60%	37%	0.001
Histology serious	66%	55%	0.095
Mean size largest lesion (cm)	6.6	7.8	0.029
≤2 sites of disease	82%	53%	0.001
CR to first-line chemo	46%	30%	0.013
Days since diagnosis (mean)	993	647	0.0003
Days since last chemo (mean)	406	215	0.0003

Following stepwise logistic regression, 4 factors remained significant at p < 0.05: age, number of disease sites, time since last chemo and performance status. Since all pts received P, no conclusion can be drawn regarding its impact on LTS, but these data suggest pt and disease characteristics at the time of initiation of 2nd or 3rd line OVCA treatment have an important effect.

533 POSTER

Independent radiological review of a phase III study of topotecan versus paclitaxel as second-line therapy in advanced epithelial ovarian cancer

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Purpose: To independently review claimed responses in a randomised, multicentre trial of topotecan (T) vs. paclitaxel (P) for advanced epithelial ovarian cancer (AEOC).

Methods: 226 patients (pts) with bidimensionally measurable AEOC, who had failed prior platinum-based therapy, were randomized to receive either T (1.5 mg/m²/d × 5 as a 30 min. inf. q 21 d) or P (175 mg/m²/d as a 3 h inf. q21 d). Pts who progressed or whose best response was stable disease after 6 courses were eligible to receive the alternate regimen. Radiographs or scans for claimed responses were reviewed by an independent radiologist.

Results:

Randomised Treatment	Topotecan		Paclitaxel	
	No. randomised	No. Switched to P	No. randomised	No. Switched to T
No. of pts	112	60	114	48
Claimed responses	38 (37.9%)	6 (10%)	28 (24.6%)	2 (4.2%)
Confirmed responses	23 (37.9%)	6 (10%)	16 (14.0%)	2 (4.2%)
No. rejected	15	0	12	0
% Rejected of claimed	39.5%	0%	42.9%	0%

Independent radiological review rejected 35% of responses; reasons for rejection included misinterpretation of normal structures & measurement errors.

Conclusions: T is an active agent in AEOC & although independent radiological review reduces the response rate it verifies the accuracy and