8035 POSTER

The Combination of Weekly Carboplatin and Paclitaxel is Active and Tolerated for the Treatment of Advanced Ovarian Cancer in Elderly Patients

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Background: Platinum/taxane doublets have long been considered the standard treatment regimen for advanced-stage ovarian cancer. Common side effects seen with the use of these drugs include gastrointestinal symptoms, myelosuppression and neurological toxicity. The purpose of this study was to evaluate the feasibility, effectiveness, toxicity and quality of life of a weekly schedule, containing carboplatin and taxanes in elderly patients.
Methods: From January 2009 to December 2010 24 patients (pts) with advanced ovarian cancer were included in the study. Median age was 74 years, and PS was 1, 2 and 3 in 15, 6 and 3 patients respectively. The pts received carboplatin AUC 2 (days 1, 8, 15), and paclitaxel 80 mg/m^2 (days 1, 8, 15) of a 28-day cycle. Primary endpoints were response rate, progression-free survival and overall survival. The results were retrospectively analyzed according to feasibility, toxicity (National Cancer Institute Common Toxicity Criteria) and quality of life (QoL).
Results: All patients were evaluable for the primary endpoint. The overall response rate was 80% (14 complete responses, 5 partial responses); the median survival has not yet been reached after a median follow-up of 24 months. Toxicity was: neutropenia grade 2/3 (33.3%); nausea grade 2 (40%); grade 1 vomiting (5%). No patient reported a worsening of QoL to report the side effects of treatment.
Conclusions: A weekly carboplatin and paclitaxel regimen is highly active for women with advanced-stage ovarian cancer. The regimen is well tolerated in elderly patients.

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The Value of the Risk of Ovarian Malignancy Algorithm (ROMA) as a Predictor of Platinum Resistance and Survival for Ovarian Cancer Patients

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Background: A Risk of Ovarian Malignancy Algorithm (ROMA) based on Human Epididymis Protein 4 (HE4) and CA125 has been developed and reported to categorize women with a pelvis mass into high or low risk of ovarian malignancy. Originally, the ROMA score was developed for diagnostic purposes but the clinical application for HE4 for other purposes such as a predictor of platinum resistance has not been investigated. The objective of the present study was to change the diagnostic ROMA score and develop a new prechemotherapy "ROMA" score. This new Risk of Platinum resistance Algorithm (ROPA score) score was developed for prediction of platinum resistance and prognosis.
Material and Methods: Serum from 170 patients with newly diagnosed ovarian cancer was analyzed for CA125 and HE4 using ELISA assays. The new ROPA score at baseline (just before initiation of chemotherapy) was developed incorporating HE4 and CA125 into an algorithm resembling the algorithm used for the diagnostic ROMA score. Samples were collected just prior to first line chemotherapy and all patients were treated with carboplatin/paclitaxel combination chemotherapy. All patients signed informed consent and permission was obtained from the relevant regulatory authorities.
Results: The ROPA score before initiation of chemotherapy was to some extent able to predict platinum resistance depending on the cut off level for specificity and sensitivity. At specificity level of 75% the sensitivity for platinum resistance was 60% for the ROPA score at baseline before chemotherapy. Increasing ROPA score was in multivariate survival analysis (adjusted for age, FIGO stage, histology, histological grade and residual tumour) negatively associated with progression-free survival (HR = 4.7, 1.3–17.1, 95% CI, p = 0.020) and overall survival (HR = 6.3, 1.3–31.6, 95% CI, p = 0.025).
Conclusions: Increasing ROPA score calculated from a serum sample just before initiation of chemotherapy seems associated with platinum resistance and decreased progression-free and overall survival.

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Linking XRCC1 Arg399Gln and GGH −401C>T Polymorphisms to Cervical Cancer Risk

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Introduction: Cervical cancer is still a key health issue worldwide. *X-ray Repair Complementing Defective Repair in Chinese Hamster Cells 1* (*XRCC1)* codifies a scaffold protein in Base Excision Repair pathway, through which it regulates other DNA repair enzymes. *Gamma Glutamyl Hydrolase* (*GGH)* regulates folate intracellular reserves. It is an important regulatory enzyme since folate has been involved in epithelial carcinogenesis.
Objective: With this study, we intended to explore what is the influence of *XRCC1* Arg399Gln and *GGH* −401C>T genotypes in conditioning cervical cancer risk.
Methods: DNA samples were extracted from peripheral blood cells of 581 patients with cervical disease and 334 healthy controls. The XRCC1 and GGH polymorphisms were evaluated through Real-Time PCR. The odds ratio (OR) and its 95% confidence interval (CI) were calculated as a measure of the association between genotypes and cervical cancer risk.
Results: Concerning *GGH* −401C>T polymorphism, we found a protective role for advanced cervical cancer development. Our results demonstrated that patients carriers of the variant T allele present 30% lower risk of advanced disease according to grouped genotype analysis (CC/CT Vs TT, IIB+III+IV Stages: OR=0.696, 0.541–0.897 95% CI, p = 0.002). Regarding *XRCC1* Arg399Gln a statistically significant association with cervical cancer risk was not observed (p = 0.842). Additionally, no association was found neither for grouped genotypes analysis (GG Vs A carrier) (p = 0.797), nor for cervical cancer stages (p = 0.567).
Discussion/Conclusions: We postulated that *GGH* over-expression could disturb folate and cell metabolism for which folic acid is essential. Since tumour cells should not be able to survive with sub-optimal folate levels, they could putatively be eliminated by apoptosis before advanced stages start to develop.

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Lymphopenia is an Independent Prognostic Factor in Ovarian Cancer and Could Be Associated With Immune Activation

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Background: The interaction between the host immune system and tumoral cells plays a major role in tumour progression. We recently showed that lymphopenia is an independent prognostic factor associated with poor outcome in a large series associating metastatic breast cancer, sarcomas and lymphomas patients [1]. Here the impact of lymphopenia on ovarian cancer (OC) patients was investigated.
Materials and Methods: A retrospective study on 146 patients treated for epithelial OC was conducted in Centre Léon Bérard, Lyon, France, between 1992 and 2009 to investigate the impact of lymphopenia on outcome. In addition a prospective study was conducted on 50 newly diagnosed OC patients comparing the percentage of activated $CD4^+$Tcells ($CD3^+CD4^+CD25^{int}$) and memory $CD4^+$T cells ($CD3^+CD4^+CD45RO^+$) evaluated by flow cytometry in lymphopenic and non-lymphopenic and the plasmatic levels of pro-inflammatory cytokines measured by multiplex ELISA.
Results: Median levels of lymphocytes were correlated with advanced FIGO stages (III/IV) when compared to early stages (I/II, $p = 0.04$). By using a cut-off of 1000/mm3, 13.7% of patients presented lymphopenia. In multivariate analysis of overall survival, in addition to "well known" prognostic factors (such as stages and residual disease), lymphopenia was an independent prognostic factor associated with short survival (HR = 2.24, $p = 0.02$). We hypothesized that lymphopenia is due to chronic immune activation. Our preliminary datas showed that lymphopenic patients present increased levels of activated $CD4^+$Tcells and memory $CD4^+$T cells among total lymphocytes when compared to non-lymphopenic patients. Comparison of plasmatic levels of pro-inflammatory cytokines, in particular IL-6 and TNF-α measured by multiplex ELISA in lymphopenic and non-lymphopenic patients are on-going and will be presented in the ESMO annual meeting.

Conclusions: Lymphopenia is an independent prognostic factor for survival in first-line treated OC and its physiopathology need to be investigated.

References

[1] Ray-Coquard et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res. 2009 Jul 1; 69(13): 5383−91.

8039 POSTER

New Dendritic Cell Vaccine Therapy Approach − Randomized Phase I/II Study in III-IV Stage Ovarian Cancer Patients

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Background: Currently, extensive studies to improve the immunotherapy approach based on DC-vaccine have been performed. Great emphasis is paid to finding new more efficient ways to load DC with tumour antigens. Our preclinical findings indicate that the lysate from tumour cells exposed to B.subtilis B-7025 cytotoxic lectins (LTCCL) used for DC loading is a very effective and promising approach. We report results of a phase I/II trial in advanced ovarian cancer (AOC) patients treated with DC pulsed with LTCCL.
Objective of the study: To examine clinical and immunological effects of specific immunotherapy with autologous DC loaded with LTCCL or conventional lysate of tumour cell (LTC) in advanced AOC treatment.
Patients and Methods: Eighty-one patient with III-IV stage AOC, ECOG 0−1, without autoimmune disorders were enrolled into randomized clinical trial. All patients received cytoreductive surgery and 6 courses of adjuvant polychemotherapy (PCT) on CP regimen (cisplatin 100 mg/m^2, cyclophosphan 800 mg/m^2). 41 patients after PCT had received DC-therapy (4−9x10^6 per injection). This group was divided into 2 subgroups: patient who received DC loaded with LTC (1 s/g) and patients who received DC loaded with LTCCL (2 s/g). Comparable groups and subgroups were similar by age of the patients, histology type of tumours, stages, volumes of surgical intervention and adjuvant chemotherapy. In the trial were used autologous DC of monocytic origin with expression of surface markers CD86 and HLA-DR at least 70%, CD83−50% obtained by flow cytometry. DCs were injected i.v. in 1−2 courses. One course consisted of 5 injections with one-month interval. Clinical and immunological monitoring of DC-vaccine therapy was performed. Special attention was focused on antigen specific cellular antitumour immune response.
Results: DC vaccine therapy was well tolerated without significant toxicity. DC vaccine therapy has improved of 1−3-year survival of patients. 1-year survival of 1 s/g patients was 88.8±3.7% and 2 s/g − 92.9±8.3 versus 80.1±3.4% in control group ($p < 0.05$). 2-year survival of patients in 1 and 2 s/gs was 47.8±4.5% and 53.1±8.5 respectively versus 20.5±4.7% in control group ($p < 0.01$). Overall survival of AOC patients with DC vaccine therapy for 3 year was: 1s/g − 26.7±5.6% and 2s/g − 39.8±8.7% versus 13.2±5.4% in control group. 95% of patients showed significant antigen specific immune response after 3−5 DC-vaccinations. In responding to DC-vaccination patients, immunotherapy significantly boosted the IFN-γ and IL-2 producting T-cell response to autologous tumour challenge. Moreover, the increased functionality of T-cells, indicated by increased expression of markers for CTL activation, differentiation and proliferation was revealed.
Conclusions: There was clear evidence of clinical benefit of vaccine therapy by DC pulsed with LTCCL for AOC patients. This approach warrants further study.

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Diagnostic and Prognostic Significance of CA125 and HE4 in Ovarian Cancer Patients

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Introduction: Epithelial Ovarian cancer (EOC) is the most frequent cause of death from gynaecological cancer, being characterized by few early symptoms, presentation at an advanced stage and poor survival. At the moment, CA125 is the unique biomarker used for EOC diagnosis. Therefore, there is a pressing need to develop new methods for early detection and prognosis. The aims of this study were to investigate: a) the diagnostic performances of CA125 and HE4; b) the association of CA125 and HE4 with the established EOC clinicopathological prognostic characteristics; c) the value of CA125 and HE4 in predicting overall survival (OS), disease-free survival (DFS) and progression free survival (PFS) for EOC patients.
Material and Methods: The study included 114 EOC patients, 131 patients with ovarian benign cysts, 34 patients with endometriosis and 140 healthy controls. Pre-operative serum samples were analyzed for CA125 and HE4 by a chemiluminescent microparticle immunoassay on automated ARCHITECT instrument (Abbott Diagnostic Division, Chicago, IL). Cutoff value was 35 U/ml for CA125 and it was 70 pM (in pre-menopausa) and 140 pM (in post-menopausa) for HE4.
Results: Serum HE4 and CA125 levels in EOC patients were significantly higher compared with healthy controls, endometriosis and ovarian cysts (all $p < 0.001$). Comparison of CA125 and HE4 at set cutoff showed that CA125 levels were above the threshold values more frequently than HE4 in EOC and in endometriosis patients. CA125 and HE4 values were positively associated with FIGO stage, histological grade, lymph node involvement, residual tumour after cytoreductive surgery, ascites and positive peritoneal cytology (all $p < 0.05$). In univariate analysis, CA125 and HE4 levels were significant associated with OS, DFS and PFS (all $p < 0.02$). Multivariate analysis showed that HE4, but not CA125, was an independent prognostic factor for OS, DFS and PFS (all $p < 0.02$).
Discussion: Our data show that CA125 is more sensitive than HE4 for EOC diagnosis, whereas HE4 is more specific than CA125 for the discrimination of endometriosis from malignant diseases. The combination of CA125 and HE4 will improve the differential diagnosis between subjects with different ovarian pathologies. The positive correlation of CA125 and HE4 levels with other established prognostic factors suggests that CA125 and HE4 could be involved in tumour aggressiveness. Finally, for the first time, we find HE4 as an independent prognostic factor in EOC patients.

8041 POSTER

Relevance of Gamma-glutamyltransferase − a Marker for Apoptotic Balance − in Predicting Tumour Stage and Prognosis in Cervical Cancer

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Background: Recent large epidemiologic population-based studies identified gamma-glutamyltransferase (GGT) as a marker for increased cervical cancer incidence. Furthermore, high levels of GGT seem to increase the risk of progression of high-grade cervical dysplasia to invasive carcinoma. Therefore, we evaluated the association between pre-therapeutic serum GGT levels, tumour stage and prognosis in patients with cervical cancer.
Materials and Methods: In this multi-center trial, pre-therapeutic GGT levels were examined in 692 patients with cervical cancer. GGT levels were correlated with clinico-pathological parameters. Patients were assigned to previously described GGT risk groups and uni- and multivariate survival analyses were performed.

Table 1. Survival analyses of 692 patients with cervical cancer.

	Disease-free survival			Overall survival		
	Univariate[1,2]	Multivariate[3]		Univariate[1,2]	Multivariate[3]	
	P-Value	*P*-Value	HR (95% CI)	*P*-Value	*P*-Value	HR (95% CI)
Tumour stage (FIGO I vs. II vs. III vs. IV)	<0.0001	<0.0001	2.0 (1.6−2.5)	<0.0001	<0.0001	2.0 (1.5−2.5)
Lymph node involvement (negative *vs.* positive)	<0.0001	<0.0001	2.5 (1.7−3.9)	<0.0001	<0.0001	2.9 (1.8−4.7)
Histological grade (G1 *vs.* G2 *vs.* G3)	0.001	0.02	1.7 (1.2−2.3)	0.003	0.046	1.5 (1.1−2.2)
Patients' age	0.001	0.5	1.0 (0.9−1.0)	0.001	0.7	1.0 (1.0−1.1)
GGT groups (A and B *vs.* C and D)	0.01	0.7	1.1 (0.7−2.0)	<0.0001	0.3	1.4 (0.7−2.6)
Histopathological Type (Squamous cell carcinoma *vs.* Adenocarcinoma)	0.04	0.3	1.3 (0.8−2.1)	0.05	0.06	1.7 (1.0−2.9)

[1]Log rank test; [2]univariate Cox-regression analysis; [3]multivariate Cox-regression analysis, HR = Hazard Ratio, 95% CI = 95% Confidence Interval; GGT = g-glutamyltransferase.

Results: GGT serum levels were associated with FIGO stage ($p = 0.002$), but not with lymph node involvement ($p = 0.2$), histological grade ($p = 0.7$)