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

References

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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.

8040 POSTER

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 ($p = 0.7$)

and type (p = 0.8). Higher GGT levels were found in advanced tumour stages (FIGO I *vs.* II *vs.* III *vs.* IV, p = 0.002). High-risk GGT group affiliation (p = 0.01 and p < 0.0001) was associated with impaired disease-free and overall survival in a univariate analysis, but not in a multivariable regression model (p = 0.7 and p = 0.3) (Table 1). We further investigated the association between prognosis and GGT and observed a linear correlation between GGT and prognosis. Therefore we were not able to identify a clear prognostic cut-off value for GGT in patients with cervical cancer.
Conclusion: High GGT − a marker for apoptosis and cervical cancer risk − is associated with advanced tumour stage in patients with cervical cancer.

8042 POSTER

Nuclear Y-box Binding Protein-1 Expression, a Predictive Marker of Prognosis, Is Correlated With Activated Signal Transducer and Activator of Transcription-3 Expression and Survival in Cervical Squamous-cell Carcinoma

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Background: The Y-box binding protein-1 (YB-1) is a member of the cold shock protein family and functions in transcription and translation. Many reports indicate that YB-1 is highly expressed in tumour cells and is marker for tumour aggressiveness and clinical prognosis. The potential role of activated signal transducer and activator of transcription-3 (STAT3) was pursued to address the underlying mechanism for YB-1-mediated survival. We have previously reported that STAT3 expression in cervical squamous-cell carcinoma acts as predictor of poor prognosis. Here, we examined whether nuclear YB-1 expression is associated with STAT3 expression and survival.
Materials and Methods: The immunohistochemical analysis of nuclear YB-1 expression was performed on tissues from 117 cervical squamous-cell carcinoma patients who underwent extended hysterectomy and pelvic lymphadenectomy and the association of nuclear YB-1 expression with several clinicopathological factors including STAT3 expression and survival was investigated.
Results: Nuclear YB-1 expression was observed in 24 of 117 (20.5%) cases and was correlated with deep stromal invasion, and STAT3 expression by Fisher's exact test. Kaplan–Meier survival analysis showed that nuclear YB-1 expression was statistically indicative of a poor prognosis for progression-free survival, but not overall survival by log-rank test. By multivariate analysis, lymph node metastasis, STAT 3 expression and nuclear YB-1 expression were independent prognostic factors with regard to progression-free survival.
Conclusions: These data showed that nuclear YB-1 expression, a predictive marker of prognosis, is correlated with STAT3 expression and survival in cervical squamous-cell carcinoma.

8043 POSTER

ERCC1 Expression Predicts Response and Survival in Locally Advanced Cervical Carcinoma Patients Treated With Concurrent Chemoradiotherapy

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Background: No suitable biological marker has been identified in patient with locally advanced uterine cervical cancer treated with concurrent chemoradiotherapy, although there is growing demand in clinical practice for individualized treatment planning. The aim of this study was to investigate whether ERCC1 expression predicted tumour response and survival in uterine cervical cancer patients who had been treated with cisplatin-based concurrent chemoradiotherapy.
Materials and Methods: Fifty patients with stage II-III invasive squamous cell carcinoma of the uterine cervix who were treated with concurrent chemoradiotherapy were enrolled. ERCC1 expression was assessed by immunohistochemistry from pretreatment cervical biopsy tissues.
Results: Of the 50 tumours examined, 16 (32%) were classified as ERCC1-positive expression and 34 (68%) as ERCC1-negative expression. Patients with ERCC-negative expression had a significantly higher complete response (33/34, 97.1%) than patients with ERCC1-positive expression (12/16, 75.0%; $P = 0.015$). The 5-year disease-specific survival rates of the ERCC1-positive and -negative groups were 43.8% and 76.5%, respectively ($P = 0.011$). The 5-year overall survival for the ERCC1-positive and -negative groups was 50.0% and 85.3%, respectively ($P = 0.008$). Multivariate analyses showed that ERCC1-negative expression (HR, 0.293; 95% CI, 0.100–0.863; $P = 0.026$) was an independent risk factor predicting the disease-specific survival of the patients. For overall survival, ERCC1-negative expression was still an independent prognostic factor ($P = 0.036$).
Conclusions: These results suggest that the ERCC1 expression patterns in pretreatment specimens can be used to predict the clinical outcome, including the tumour response and survival in patients treated with cisplatin-based chemoradiotherapy for locally advanced uterine cervical cancer.

8044 POSTER

Prognostic Role of Microvascular Density (MVD), VEGF, HIF-1, and EGFR Expression in Women Suffering From Locally Advanced Cervical Cancer (LACC) Treated With Chemoradiotherapy in Colombia − ONCOLGroup Study

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Background: Recent data series showed that cervical carcinoma is the second leading cause of death among women in Colombia.
Methods: We want to describe the prognostic value of microvascular density (MVD), VEGF, HIF1 and EGFR in women suffering from LACC treated with chemoradiotherapy followed by high dose rate brachytherapy (HDRB). Overall response rates (ORR), progression-free survival (PFS) and overall survival (OS) were estimated.
Results: Sixty-one patients were included (mean age 52±10-yo); all of them had LACC (2.3% 2A/47.5% 2B/4.9% 3A/37.7% 3B/3.3% 4A/3.3% not defined), a tumour mean size of 6.4 cm (SD ± 1.8 cm) and HPV infection in 46% of the cases. Fifty-eight patients (95%) had a squamous pattern, two were adenocarcinomas and >50% presented moderated or poorly differentiated neoplasias. All of them were treated with chemotherapy (transitory interruption in RT was documented in 19% due to toxicity and in 21.4% of cases by other causes; mean cycles of platinum administered during radiotherapy was 4.8±1.0) and HDRB (77% completed all planed treatment). The median PFS and OS was 6.6-mo (range, 4.0−9.1) and 30-mo (range, 11−48) respectively. None of the variables had a positive effect on PFS, whilst multivariate analysis revealed that VEGF (p = 0.026) and EGFR expression levels (p = 0.030) and less than 6 cm tumour volume (p = 0.02) positively influenced the OS.
Conclusions: Classifying LACC patients treated with cisplatin-based chemoradiotherapy by protein expression had a positive influence on prognosis.

8045 POSTER

Fused Toes Homolog is a Novel Oncoprotein Involved in Uterine Cervical Carcinogenesis and a Potential Diagnostic Marker for Cervical Cancer

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Background: The high incidence and fatality rate of uterine cervical cancer warrant effective diagnostic and therapeutic target identification for this disease. Here, we have found a novel oncoprotein FTS (Fused Toes Homolog), which is involved in cervical cancer pathogenesis.
Materials and Methods: For Immunohistochemical analysis of FTS total 49 formalin-fixed paraffin-embedded specimens of human cervical CIN and carcinoma tissues were stained. For in vitro study, HeLa, ME180, SiHa, and CaSki cells were used.
Results: Immunohistochemical analysis of human cervical biopsy samples revealed that the expression of FTS is absent in normal cervical epithelium but progressively overexpressed in human cervical intraneoplastic lesions (CIN-I to CIN-III), this characteristic phenomenon put this protein, a potential diagnostic marker for the screening of early neoplastic changes of cervix. Using FTS-specific small hairpin RNA (shRNA) in cervical cancer cells, we determined a specific role for FTS protein in, cervical neoplasia. Targeted stable knock down of FTS in HeLa cells led to the growth inhibition, cell-cycle arrest, and apoptosis with concurrent increase in p21 protein. FTS effectively represses the p21 mRNA expression in dual luciferase assay which indicates that p21 is transcriptionally regulated by