968 PUBLICATION

Expression of syndecan-1 in endometrial cancers and its functions

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Syndecan-1 is one of major proteoglycans on cell membrane. It has been reported that syndecan-1 plays critical parts in a plethora of cell functions, including embryogenesis, cell migration, wound healing, and cancer progression. Often it is believed that the loss of syndecan-1 is correlated with aggressive phenotypes of cancer cells and poor prognosis. However, there have been contradictory reports regarding the correlation between level of syndecan-1 expression and cancer phenotype in other cancer cases, notably in breast cancer. Therefore, the expression and the loss of syndecan-1 may be tissue specific and thus display different functions of syndecan-1. In cases of endometrial cancer, there have been only two reports about syndecan-1 expression in the cancer tissue, which characterized the cancer with the loss of syndecan-1 in higher cancer grade without mentioning molecular and cellular functions of syndecan-1. Nevertheless, we report the contradictory results after examining 43 different tissue samples against syndecan-1 collected from 1995 to 2003. Our findings support significant close relationships of the syndecan-1 overexpression to the higher tumor grade ($p \leqslant 0.043$) and surgical grade ($p \leqslant 0.039$) along with increased myometrium invasion depth ($p \leqslant 0.012$), and lymphatic invasion ($p \leqslant 0.009$). In order to support the results, we have set an In-Vitro model with a well-differentiated endometrial cancer cell line HEC-1A, expressing syndecan-1 at a low level. Treatment of small hairpin antisense RNA (shRNAi) against syndecan-1 down-regulated the growth of HEC-1A dramatically while the overexpression of syndecan-1 caused more rapid growth of the cancer cells in both 96 well plates and agarose suspension culture.
In addition, the silencing of syndecan-1 decreased the cell invasiveness by half into matrigel in the Boyden chamber compared to the cells transfected with control shRNAi. Moreover, we have found after running a nano 2-D chromatography analysis of the whole cell protein extracts that the silencing caused different profiles of expressed proteins in the cancer.
In conclusion, it is thought that the syndecan-1 expression in the endometrial cancer cells has a linear correlation to the progression of carcinogenesis, and roles of syndecan-1 are thought to help cells survive and proliferate by regulating its down stream gene expressions.
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969 PUBLICATION

CYP2E1 polymorphism and susceptibility to cervical cancer

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Background: Cervical cancer (CC) causes about 190.000 deaths annually, being one of the most common causes of death in women. Among the risk factors for CC, both genetic and environmental factors have an important role. In fact, infection with HPV is the major factor of risk in the development of CC, although other co-factors (with genetic, environmental or immunological origin) may interfere in the multi-stage process that leads to the disease. There is commonly accepted that this is a continuum process, beginning with the infection with HPV in normal cervix, passing for a stage of low grade lesions (LSIL) and high grade lesions (HSIL) and ending in an invasive carcinoma. Some of these co-factors are the tobacco smoke, dietary factors and other sexually transmitted diseases.
CYP2E1 interferes in the metabolism of several exogenous and endogenous factors, such as N-nitrosamines and alcohol, promoting the formation of DNA adducts. The role of tobacco smoke is well documented in the aetiology of CC. The enzyme activity is also described as being modulated by several immunological factors, whose importance in the CC development and progression is under investigation.
Methods: There were analysed a total of 207 cases of women with pathologies of the uterine cervix (59 presented LSIL or HSIL lesions, 122 invasive squamous cell carcinoma (ICC) and 8 presented adenocarcinoma. In the other cases it was not possible to determine the histological status) and 273 healthy controls. The genotypic analysis was performed using PCR-RFLP technique.
Results: We observed that the presence of C allele (genotype CC/CD) is higher in cases (27%) than in controls (18%) and this different was statistically significant ($p = 0.029$). Although we did not find any statistical differences between controls and women with ICC, we observed that the C allele may have a protective role in the development of cervical lesions, that may lead to invasive carcinoma (OR = 0.08, 95% IC 0.012–0.65; $p = 0.001$). The analysis was stratified according to patient's median age.
Conclusions: The allele C may have an important role in the development of the initial lesions of the uterine cervix. This may be important due to its interference in the metabolization of compounds of the tobacco smoke and dietary factors.

970 PUBLICATION

High cyclooxygenase-2 expression is related with local recurrence in cervical cancer treated with postoperative radiotherapy

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Background: The purpose of this study was to examine the relationship between local recurrence or distant metastasis and COX-2 expression in cervical cancer patients treated with postoperative radiotherapy. A clinicopathologic study was performed on 56 patients.
Methods and Material: Formalin-fixed, paraffin-embedded tumor biopsies were stained for Cyclooxygenase-2 (COX-2). COX-2 expression was evaluated by a semiquantitative score and by calculating the labelling index, i.e. defining the ratio between stained and negative cells, for each sample. Clinical factors such as stage, grade, tumor size and radiotherapy dose were also evaluated.
Results: The median COX-2 labelling index (LI) was 58.8%. In terms of local tumor control none of the 28 patients with COX-2 LI below the median developed a local recurrence, whereas in 3 patients (out of 27) with COX-2 LI above the median a local recurrence war observed ($p = 0.07$). Although a high percentage of distant metastases was observed (21%) in this relatively small patient cohort, no relationship according to high COX-2 expression could be demonstrated. Among the clinicopathologic factors stage and grade were found to closely correlate with COX-2 expression.
Conclusion: These findings indicate that increased expression of COX-2 portends an increased local treatment failure in patients with invasive carcinoma of the cervix treated with postoperative radiotherapy. Because COX-2 is an early-response gene involved in angiogenesis and inducible by different stimuli, these data my indicate opportunity to intervene with specific inhibitors of COX-2 in carcinoma of the cervix.

Haematological Malignancies

Oral presentations (Thu, 3 Nov, 8.30–10.30)

Treatment of malignancies in children and adults – long term side effects

971 ORAL

Adolescent cancer survival in France

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To study survival of adolescents diagnosed with cancer in France.
Patients and methods: Data from the FRANCIM network of French population-based cancer registries covering 10% of French population were used to examine patterns of survival of adolescents diagnosed with a cancer (excluding basal cell carcinoma). Data of all the patients aged 15 to 19 recorded in these registries over a 10-year period, (1988 to 1997) were studied. Follow-up information (cancer recurrence or progression, death from treatment side effects or from the cancer itself) became available after actively searching the medical records of each hospital in which patients had been treated.
Results: Five-year OS and DFS for all cancers pooled ($n = 648$) was respectively 74.2% (95% CI: 70.8–77.6) and 68.9% (95% CI: 65.3–72.5). OS and DFS at 5 years were respectively 100% and 100% for thyroid carcinoma (35pts), 85% and 90% for Hodgkin disease (98pts), 95% and 89% for melanoma (63 pts), 89% and 82% for germ-cell tumors (89 pts), 69% and 68.5% for soft-tissue sarcoma (49 pts), 64% and 60.9% for NHL (49pts), 63% and 55.9% for CNS tumors (67pts), 56% and 47.6% for malignant bone tumors (68pts), 45% and 45% for ANLL (20pts), and 42% and 33.8% for ALL (47pts).

Between the two 5-year periods (1988–92 vs. 1993–97), 5-year OS rates increased by 10% (p = 0.05). (Males were 2.0 times more likely to die than females (95% CI: 1.5–2.7), with OS respectively at 67.4% (95% CI: 62.4–72.4) and 82.4% (95% CI: 78.0–86.8) at 5 years (p < 0.001).
Conclusion: Compared with pediatric series, poor results in acute lymphoblastic leukemia and malignant bone tumors have to be highlighted, and deserve further studies concerning the type of regimens used for these patients

972 ORAL

Ifosfamide vs cyclophosphamide: long term gonadal effects in 116 male survivors of childhood cancer

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Purpose: to compare the effects of ifosfamide vs cyclophosphamide in infertility and long term gonadal damage in male survivors of childhood cancer.
Patients: 116 males were evaluated after treatment of a Soft tissue sarcoma (51), Osteoasarcoma (27), Ewing (7), Lymphoma (28), other (3). 57patients received ifosfamide as unique alkylating agent and the other 59 received cyclophosphamide as the other unique alkylating agent between 1984 and 2000. Median age at treatment was 10 years (0–18yrs). Median interval after the end of the treatment was 9.5 years (4.1–19.6 yrs), median age at evaluation was 20.5 years (17.5–31.3 yrs). Median dose of ifosfamide was 51g/m2 (18–114), median dose of cycle was 8.3 g/m^2 (4.6–22). Age at treatment and at evaluation were similar in both groups.
Methods: Evaluation was based on basal FSH measurement known for its correlation with spermatogenesis. LH and testosterone were also measured in most of the patients.
Results: All males but two (17.5 and 22.7 yrs) had normal testosterone levels. FSH was above laboratory upper limit in 28 of the 59 males (47.5%) treated with cyclophosphamide and was within the normal range in 56 of 57 patients (98%) treated with ifosfamide. One patient who received 54 g/m2 of ifosamide fathered two children, another patient who received 51 g/m^2 had a boy.
The risk of abnormal FSH increased with the cumulative dose of cyclophosphamide: only 2/16 boys (12%) who received more than 12 g/m^2 had a normal dosage of FSH, while 29/43 (67%) of the boys who received lower doses of cyclo did so.
Conclusions: These results show a low risk of gonadal dysfunction in men exposed to ifosfamide (median dose 51 g/m^2) compared to the results for males treated with cyclophosphamide. Additional patients are under evaluation.

973 ORAL

Longitudinal cardiac follow-up in doxorubicin-treated bone tumour survivors

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Background: Previously we performed cardiac assessments (CA) in anthracycline-treated long-term bone tumour (BT) survivors at median 8.9 (CA-1) and 14.1 (CA-2) years post-treatment. Between CA-1 and CA-2 systolic function did not deteriorate. At CA-2 heart rate variability (HRV) was progressively impaired compared to CA-1 (Med Pediatr Oncol 2002;39:86). The aim of the current study (CA-3) was to re-assess the cardiac status up to 27 years post-treatment.
Patients and methods: The original cohort consisted of 31 patients. 22 of them participated in CA-1, CA-2 and CA-3. Causes for non-participation in CA-2 or 3: death from congestive heart failure (n = 1); death from second malignancy (SMT; n = 1); thoracic irradiation for SMT, hence exclusion (n = 2); terminal neurodegenerative disease (n = 1); refusal (n = 4). Median age at diagnosis was 17.8 (10–45.8) years. At CA-3 median age was 39 (27–59) years, follow-up 22 (15–27.5) years. All patients were treated with Rosen's T5 or T10 protocol between 1977–1990; they received a median cumulative dose of doxorubicin of 360 (225–550) mg/m^2. Cardiac function was assessed by history, physical examination, 24-hrs ambulatory ECG and 2D-colour Doppler echocardiography. Shortening fraction (SF) < 0.29 and/or wall motion score index (WMSI; only performed in CA-3) >1.0 represented systolic dysfunction. E/A ratio (E/A; performed in CA-2 and CA-3) < 1.0 represented diastolic dysfunction. Statistical analyses were done by non-parametric tests.
Results: None of the 22 patients had signs of clinical heart failure. At CA-3 6/22 (27%) had a decreased SF versus 2/22 (9%) at CA-2 (p = 0.02). All 6 patients with a decreased SF in CA-3 also had an abnormal WMSI: 2/6 had a diffuse wall motion abnormality and 4/6 had a regional wall motion abnormality. A decreased E/A was more frequently found in CA-3 compared to CA-2: 10/22 (45%) versus 4/22 (18%; p = 0.02). We found no correlation between SF, WMSI or E/A ratio and cumulative dose of doxorubicin, age at diagnosis, current age or duration of follow-up. Although not significant, compared to an age-matched control group, all HRV variables shifted towards sympathetic domination.
Conclusions: During a prolonged follow-up period up to 27 years doxorubicin-treated BT-survivors developed progressive systolic and diastolic cardiac dysfunction. The finding of regional wall motion abnormalities in 4 patients suggests ischemic infarction. In addition, all patients showed progressive deterioration of HRV variables.

974 ORAL

Cardiovascular morbidity in long-term survivors of Hodgkin lymphoma (HL)

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Background: Cardiovascular disease (CVD) causes excess morbidity and mortality in survivors of HL. The objective of the study was to assess the incidence of CVD in long-term survivors of HL after primary treatment stratified by treatment and age at treatment.
Material and methods: We assessed the incidence of CVD in 899 5-year survivors of HL treated before the age of 41 years in the Netherlands Cancer Institute, Amsterdam or the Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam between 1960 and 1995. Median age at diagnosis of HL was 24.7 years. 30% of the patients were treated with radiotherapy (RT) alone, 4% with chemotherapy (CT) alone, 23% with initial combined modality treatment without treatment for relapses and 43% with initial therapy including maintenance CT or initial therapy followed by salvage therapy.15% of all patients received anthracycline-containing therapy. Information on medical status was complete for 95% of the cohort. In the Netherlands, population-based incidence rates are available for several CVDs, i.e. acute myocardial infarction (MI), angina pectoris (AP), congestive heart failure (CHF), and cerebrovascular disease (CD). We compared the observed numbers of these CVDs in our HL cohort with the numbers expected based on age- and gender-specific incidence rates of CVDs in the Dutch population.
Results: After a median follow-up of 19.5 years, 159 out of 899 patients developed one or more CVDs, while only 35 were expected [RR = 4.6; 95%-CI: 3.9–5.3]. Seventy-two patients had a MI [RR = 7.9; 95%-CI: 6.1–9.9], 38 CHF [RR = 8.1; 95%-CI: 5.8–11.2] and 25 CD [RR = 3.6; 95%-CI: 2.3–5.3] The RR of all CVDs remained increased with longer follow-up. The RR of CVD was significantly lower for patients who received primary RT+CT than for patients who received maintenance therapy or salvage therapy (RRs 3.4 respectively 6.4; p = 0.01). No significant influence of anthracyclines could be demonstrated; however, the number of patients treated with anthracycline containing therapy was rather small and the median follow up only 13 years.
Conclusion: The incidence of several types of CVDs was strongly increased after treatment for HL. This risk of CVD remained elevated even after prolonged follow-up. The RR of CVD was significantly higher in patients who were treated with maintenance therapy or salvage therapy as compared to the RR in those treated with primary CT+RT only. The effect of anthracycline-containing therapy remains to be determined.