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A phase II study of capecitabine in patients who have failed first-line treatment for locally advanced or metastatic cervix cancer (MCC)

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Background: Capecitabine (Xeloda®) (X) is a TP-activated oral fluoropyrimidine, which exploits the higher concentration of its activating enzyme in cervical cancer cells compared to normal tissue, to produce 5-FU within the tumour. This study evaluated the efficacy and safety of X in MCC patients (pts) who failed first-line therapy.

Materials and methods: Efficacy was evaluated by WHO criteria and safety according to NCI CTC version 2.0. Thai and Taiwanese pts with histologically confirmed squamous cell or adenocarcinoma of uterine cervix, with ECOG ≤ 2, adequate liver and renal functions, received oral X 1250 mg/m^2 twice-daily, days 1-14, every 3 weeks. Pts responding or with stable disease (SD) after 2 cycles continued X up to 6 cycles.

Results: 45 evaluable pts (41 Thai, 4 Taiwanese) were enrolled since 2000. One year has elapsed since the last pt finished treatment (tx). Table shows baseline data and efficacy results.

	N=45
Median age (years)	48 (30-61)
Median ECOG	1 (0-2)
Prior tx:	%
Radiotherapy alone	29
Surgery + radiotherapy	11
Chemoradiation	47
Chemotherapy alone	3
Median tx duration (cycles)	4 (1-6)
ORR (95% CI) including 1 CR	13% (5-27)
SD	53%
Median response duration (months)	16
Median survival (months)	9.3 (7.1-13.7)

Updated TTP will be presented at the meeting.

The most common clinical adverse events (all grades) were hand-foot syndrome 49% (14% G3-4), diarrhea 18%, and nausea 13%. Grade 3-4 lab abnormalities were lymphopenia 20%, anemia 11%, leukopenia 4% and hyponotremia 4%.

Conclusion: In these difficult-to-treat MCC pts with limited further options, X was well-tolerated and active. Future study in earlier lines of tx and with other active agents is warranted.

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The biological relevance of the E-cadherin/catenin complex in epithelial ovarian tumours

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Background: Epithelial cadherin associates with alpha, beta and gamma catenins. This adhesion molecule plays a key role in cell polarity and differentiation. Alterations in any of these molecules result in loss of intercellular adhesion and may initiate cellular transformation.

Aim: Analyse the biological relevance of the E-cadherin-complex immunoexpression (reduced *versus* preserved) in benign, borderline and malignant tumours.

Materials and Method: Immunohistochemical E-cadherin, alpha, beta and gamma catenin was performed in 154 epithelial ovarian tumours, consisting of 17 benign, 33 borderline and 104 malignant tumours.

Results: Benign tumours, no association with histotype and immunoexpression pattern of E-cadherin/catenin complex.

Borderline tumours, E-cadherin (*p=0.014*) and alpha-catenin (*p=0.030*) immunoexpression pattern associated with histotype. Mucinous tumours associated with E-cadherin preserved phenotype. Serous tumours associated with reduced phenotype of E-cadherin and alpha-catenin.

Malignant tumours, an association between immunoexpression pattern of E-cadherin and histotype ($p<0.001$). An association between immunoexpression pattern of beta-catenin and histotype ($p<0.001$), differentiation (*p=0.02*). Mucinous carcinomas associated with preserved phenotype of E-cadherin. Serous carcinomas associated with reduced phenotype of E-cadherin. The preserved phenotype of beta-catenin associated with endometrioid carcinomas. Whereas, the reduced phenotype associated with poorly differentiated serous and clear cell carcinomas. Although, the reduced phenotype was the most frequent immunoexpression observed for all proteins of the E-cadherin/catenin complex in ovarian epithelial tumours, only beta-catenin showed a difference between benign, borderline and malignant tumours (*p=0.02*). An inverse relationship with the immunoexpression pattern of beta-catenin was observed with increasing tumour malignancy.

Conclusion: Although the reduced immunoexpression of the E-cadherin-catenin complex were observed in epithelial ovarian tumours, the immunohistochemical profile of beta-catenin is of biological relevance and may provide new insight into the biology of ovarian carcinogenesis. Since, the reduced phenotype of beta-catenin correlated with loss of differentiation and histological types known to associate with aggressive biological behaviour patterns in epithelial ovarian tumours.

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Molecular biomarkers in ovarian cancer

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Background: The expression of molecular biomarkers of apoptosis (p53, Bcl-2, Bax FasL), proliferation (Ki-67) and angiogenesis (VEGF, Flk-1, Flt-1, thrombospondin, thymidine phosphorylase (TP), and angiopoetin-2 (Ang-2)) was studied in 96 serous ovarian cancer patients (pts) III-IV stage.

Material and methods: The research was performed on paraffin-embedded blocks using standard immunohistochemical method. Slides were incubated with primary antibodies at 4^{0}C overnight, and process using visualizing system LSAB®+kit (DAKO Corp), according to the manufactures.

Results: p53 expression was observed in 54% cases, Bcl-2 in 39% cases, 0E - in 56% cases, FasL was observed in 68% cases of serous ovarian cancer. Bcl-2 expression correlated with 0E expression (p= 0.028). Mean proliferative activity of ovarian cancer (index Ki-67) was 43±32% (median - 40%). The Ki-67 index correlated with tumour grade (k = 0.3, p= 0.002). VEGF expression in tumour cells was found in 65% cases, expression Flt-1 (VEGF-R1) in 37% cases and Flk-1 (VEGF-R2) 29% cases. TP is found in tumour cells in 48% and in stromal cells in 65% cases. TP stromal cells expression reverse correlated with tumour degree (k = -0.22; p= 0.03). The patients having complete and partial response from the first phase chemotherapy with platinum-compound regimens±taxanes were more often Bax positive (63% cases) than patients with disease progression (33% cases). Bax -positive pts had progression in 76% cases (median time to progression was 17 month) and Bax-negative pts - in 87% cases (median time to progression was 12 month). Among Bax negative 64% of pts died (median was 32 months), among Bax positive - 42% of pts died (median was 85 months) (p= 0.02). Ang-2 expression was a favorable prognostic factor. 3-years overall survival was 77% in Ang-2+ pts.

Conclusion: Our results suggest that Bax and Ang-2 are the prognostic markers of chemotherapy efficacy in ovarian cancer patients.

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Clinicopathological study of treatment in patients with uterine sarcoma

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Background: Uterine sarcoma is the most aggressive and refractory disease of gynecologic malignancies and no standard treatment has been established. It seems very important to investigate their pathological prognostic factors and evaluate the adequate chemotherapy for uterine sarcomas.

Patients and Method: Multi-institutional retrospective study was conducted and 191 cases of uterine sarcoma patients were enrolled in this

study form 24 institutes (Kansai Clinical Oncology Group and the Study group of Japan Ministry of Health, Labor and Welfare on Uterine Sarcoma Treatment). One hundred and eighty-six of 191 patients (pts) diagnosed as uterine sarcoma during the last decade were eligible for retrospective analysis.

Results: The subtypes of uterine sarcoma were endometrial stromal sarcoma (ESS) in 27 pts, leiomyosarcomas (LMS) in 71 pts and carcinosarcoma (CS) in 85 pts. Seventy pts were treated by cytoreductive surgery alone and 86 pts were treated by cytoreductive surgery followed by adjuvant chemotherapy. Median progression free survival (mPFS) and median overall survival (mOS) were as follows. The mPFS of ESS, LMS, and CS were 18.4, 11.7 and 10.2 months, respectively (n.s.). The mOS were 23.6, 18.6 and 18.5 months, respectively (n.s.). Patients with LMS who had received adjuvant chemotherapy after surgery showed a trend for a longer PFS than patients who had received only surgical treatment (p=0.123, Wilcoxon test). In 30 types of chemotherapy regimens, CyVADIC (cyclophosphamide, vincristine, doxorubicin and DTIC) therapy was chosen for 28 pts and CAP (cyclophosphamide, doxorubicin and CDDP) therapy was administered for 31 pts. Platinum-based and non-platinum regimens were compared. Non-platinum regimens (39 pts) were superior to platinum based regimens (64 pts) in PFS of LMS patients with stage Ic or more advanced tumor (p=0.001; odds ratio 0.10, 95%CI: 0.015-0.664, Logrank test). New agent of irinotecan (CPT-11) weekly chemotherapy has been conducted as a pilot study in few cases and responders were identified.

Conclusion: Adjuvant chemotherapy of non-platinum regimen for LMS patients might be useful to prevent from recurrence of tumor. Considering to a few feasible results, phase II study of CPT-11 for patients with LMS and CS has been proposed.

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The impact of spontaneous apoptosis on DNA ploidy, proliferative activity, status of human papillomavirus(HPV) and treatment outcome in cervical carcinoma

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Background: To evaluate the effect of apoptosis on ploidy pattern, S-phase fraction (SPF), clinical stage, status of HPV16 & 18 and treatment outcome.

Material and Methods: Seventy five irradiated cervical cancer patients were collected for archival specimens. A minimum follow-up period of 5 years was required for all patients. Flow cytometry & polymerase chain reaction (PCR) were used to identify the status of DNA index, proliferative activity (SPF with a cut-off value of 10) and HPV 16 and 18. In situ quantification of apoptotic cells was performed by in situ Nick end labeling and Klenow DNA Fragmentation Detection Kit. The apoptotic index (AI) was calculated as percentage of apoptotic cells in the counted cells.

The semi-quantitative approach was used to identify the presence of mutant P53. The immunohistochemical staining reaction of formalin-fixed, paraffin-embedded specimen was evaluated by assessments of the overall staining intensity and by the fraction of stained cells in percentage categories.

Results: Mean (± SD) apoptotic index (AI) correlated inversely with DNA index (DI) which are 11.98 ±4.57, 8.77 ±4.49 and 7.43 ±4.96 respectively for DI value of 1, 1-1.5 and > 1.5 (P = 0.002) . A significantly high value of AI corresponded to patients with a low SPF: 15.30 ±2.35 (SPFd10) vs. 7.41 ±3.56 (SPF > 10) (P < 0.001). Status of HPV 16, 18 and mutant P53 beared no significant correlation to mean AI values (P = 0.898, 1.00 and 0.714) . Patients with clinical stage (CS) of d2b yield relatively high mean value of AI than CS of > 2b did (11.08 ±4.66 vs. 8.63 ±5.15, P = 0.038) . Increased spontaneous apoptosis induced increased treatment response, that is, AI value of 11.29 ±4.50 for 48 complete responders while only 8.36 ±5.22 in 28 patients with partial or no response to treatment (P = 0.012)

Conclusions: High proliferative activity (SPF > 10) and aneuploid pattern (DNA > 1) signified a relatively low AI value which beared no significant correlation to status of HPV 16, 18 or mutant P53. Increased spontaneous apoptosis occurred in patients with low clinical stage (f2b) and high treatment response. This, however, did not translate into a change of the status of relapse or 5-year overall survival.

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A phase II second line study of liposomal doxorubicin and carboplatin in patients with recurrent ovarian cancer with a disease free interval equal or greater than 6 months

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Liposomal doxorubicin (Caelyx) trials in relapsed/refractory ovarian cancer patients have shown to induce a clinical benefit with a reduction in several toxicities attributed to anthracyclines. A recent phase I study of the combination of carboplatin and Caelyx conducted by the above investigators has shown that carboplatin at an area under the curve (AUC) 5 and Caelyx 50mg/m2 given every 4 weeks, could be combined with acceptable toxicity. The aim of this phase II second line study is to determine the feasibility, efficacy and toxicity of Caelyx at a dose of 50mg/m2 in combination with carboplatin AUC of 5 in patients with recurrent ovarian cancer with a disease free interval equal or greater than 6 months. All patients were previously treated with platinum and taxane based regimens. Cycles are repeated every 28 days. Eighteen patients (pts) have been entered on this study to date. The median ECOG performance status (PS) is 1 (range 0-1). The median age is 58 years (range 47-75). A total of 66 cycles have been administered, with a median of 4 cycles (range1-7). Ten pts had measurable and 8 pts had evaluable disease. At this stage 10 of the 18 pts are evaluable for response. Two pts withdrew consent and 6 pts are too early for evaluation. Documented responses include 6 complete and 2 partial responses. Two pts had stable disease. Haematological toxicities include anaemia (grade I: 3 pts; grade II: 1 pt), leucopenia (grade I: 3 pts; grade II: 4 pts; grade III: 3 pts), neutropenia (grade I: 2 pts; grade II: 3 pts; grade III: 3 pts; grade IV: 3 pts) and thrombocytopenia (grade I: 1 pt; grade III: 5 pts). Febrile neutropenia or active clinical bleeding has not been documented. Non haematological toxicities include PPE (grade I: 2 pts; grade II: 5 pts; grade III: 3 pts). Nausea and vomiting (grade I- III in 11 pts), stomatitis (grade I- II in 9 pts) and aesthenia (grade I-III: 12 pts). No renal toxicity has been observed. The combination of Caelyx at a dose of 50mg/m2 with carboplatin at an AUC of 5 appears to be a active and safe second line chemotherapy regime for advanced ovarian cancer. The study is still ongoing.

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Combined radiotherapy with irinotecan (CPT-11), interferon a2b (IFNa2b) and amifostine in patients with locally advanced cervical carcinoma (LACC)

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Background: Radiotherapy (RT) constitutes a standard treatment for LACC. CPT-11 is an active chemotherapeutic agent and presents a remarkable radiosensitizing action, while IFNa2b potentiates the antiproliferative action of CPT-11 and has also been shown to be a radiosensitizing agent. Amifostine has been shown to protect against radiotherapy and chemotherapy toxicities in various indications and settings. The purpose of this study is the evaluation of the efficacy and safety of the combination CPT-11, IFNa2b and RT in LACC under the cytoprotective action of Amifostine.

Materials and Methods: Twenty-five patients with LACC stage IIB (17), IIIA (1) and IIIB (7) have been entered in the study. Median age was 57 years (range 36-75 years). The patients received standard fractionated RT (1.8 Gy/fraction, 5 days/week) for 6 weeks with a median dose of 54.7 Gy, CPT-11 30 mg/m2/ week, IV, on day 1 and IFNa2b 3 MU, SC, TIW, prior to RT. All 21 patients completed the scheduled RT. A 20 Gy additional intracavitary treatment with Cs was administered. Amifostine was administered IV at a flat dose of 500 mg prior to each RT fraction.

Results: Until now 21 patients have been evaluated with a median follow-up of 6 months (range 3-21 months). CPT-11 was administered at 90% of the scheduled dose, IFNa2b at 91% and RT at 97.5%. Amifostine was administered as scheduled, except for 2 patients to whom administration was interrupted due to emesis (1) and hypotension (1). Response to treatment was as follows: 11 patients (52.4%) achieved a clinical complete response (cCR), 9 (43%) a clinical partial response (cPR) and one showed stabilization of the disease. No relapses have been observed so far.