909 ORAL

Topotecan: Tolerability, response rate and survival associated with extended therapy in relapsed ovarian cancer – Results of a pooled analysis of 523 patients

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Topotecan inhibits topoisomerase I and is efficacious in relapsed ovarian cancer. To evaluate the long term tolerability and efficacy of intravenous topotecan for the treatment of relapsed ovarian cancer – a multivariate analysis of pooled data from 523 patients in five multicenter clinical trials was performed. Topotecan was administered as a 30 minute infusion daily for five consecutive days at a dose of 1.5 mg/m^2/day. A logistic regression analysis was performed to investigate factors associated with prolonged treatment. 29% of patients received 7 or more cycles of therapy (7–33 cycles). Patients with a performance status (PS) of 0 or 1 at baseline were 2.4 times more likely than those of PS 2 to have received 7 or more courses of treatment. The objective response rates were 43.5% for patients receiving more than 6 cycles of therapy and 5.7% for patients receiving 6 courses or fewer. In addition, 38.8% of patients on prolonged treatment experienced stabilisation disease; 22.7% of patients receiving 6 or fewer cycles also experienced disease stabilisation. The median survival was 99.7 weeks for patients who received prolonged therapy and 46.1 weeks for patients who received less than six cycles of therapy.

Topotecan was well tolerated in patients receiving long term therapy. The incidence of toxicity is similar in patients receiving six or less. Grade 3/4 neutropenia occurred in 28%/47% of cycles respectively for patients who received less than six or fewer cycles of therapy and 29%/31% of cycles for patients who received more than six cycles.

Many relapsed ovarian cancer patients are able to tolerate long term therapy with intravenous topotecan. Prolonged topotecan therapy does not appear to have cumulative toxicity and therefore extended therapy is possible. Clinical benefit of prolonged treatment requires further investigation. (Supported by SmithKline Beecham)

910 ORAL

Feasibility of an accelerated multi-cycle high-dose chemotherapy regimen including high-dose thiotepa for patients (Pts) with poor risk ovarian cancer (OC)

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OC is an appropriate target for dose-intensification. Taxol (T)/platinum produces frequent responses and survival prolongation, but only 15–25% of stage III–IV pts are cured. We previously demonstrated the feasibility of a regimen in which high-dose T and cyclophophamide (CPA) supported by filgrastim, were used as induction, and to mobilize haematopoietic progenitors (PBP) for the support of 4 cycles of 2-weekly high-dose carboplatin (CBDCA) and CPA. This regimen resulted in gross clearing of disease in 90% of patients at second look laparotomy (2LL), but only 33% achieved pathological remission (pCR). In an attempt to increase pCR, we are studying a program which includes highly dose-escalatable alkylators. Regimen (mg/m^2): Levels I–II: Cycles 1–2; CPA 3000/T 300 + filgrastim × 2. Cycles 3–5 CBDCA AUC 12 + CPA 1500 × 3. Cycle 6 Cyclo 3000 + Thiotepa (Level I-500, II-700). In Level III–V melphalan is added to Cycle 5 (80, 120, 140). Cycles I–IV are given at 2 week intervals, with 3–4 weeks between cycles 5–6.

Results: Levels I–II are completed (7 pts), Level III is under study (3 pts). Of 2 Level I pts, 1 had pCR and relapsed at 28 months (m), 1 had minimal residual disease (MRD), was resected to CR and relapsed at 7 m. At Level II, five pts with primarily inoperable (2 pts) or suboptimally debulked (3 pts) OC were treated. At 2LL, 3 pts had pCR and remain progression-free at 21+, 15+, 11+ m, 2 had MRD, and were resected to CR (1 progression-free at 33+ m, 1 relapsed at 6 m). At level III, 1 pt had clinical CR, 2LL pending. At present, the response rate is 100%, with 57% pCR. For Levels I–II, at a median follow-up of 24 m from completion of therapy, 5/7 pts are alive and 4/7 progression-free. Grade IV neutropenia and grade III–IV thrombocytopenia are universal following PBP cycles. One pt developed temporary tinnitus. There were no treatment-related deaths.

Conclusion: (1) High-dose thiotepa/CPA can be incorporated into an accelerated, multi-cycle Taxol/CBDCA/CPA-based high-dose chemotherapy regimen. (2) The regimen is safe and feasible, and (3) appears to be highly active.

911 POSTER DISCUSSION 1

Identification, characterization and signal transduction of $P2Y_2$ receptors in human ovarian cancer cell lines and ovarian cancer tissues

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Objective: At present there is poor respectively no information about expression and effector coupling of calcium-mobilizing P2Y receptors in human ovarian cancer cell lines and tissues. Identification of this receptor and characterization of its coupling in EFO-21 and 27 cell lines and ovarian cancer tissue was purpose of this project.

Methods: RT-PCR analyses with total isolated RNA, Cell Proliferation Assay, Measurement of $[Ca^{2+}]_i$ with Digital Fluorescence Microscopy System, PEt Assay.

Results: In single cells, extracellular ATP reduced a rapid spike-like rise in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) in a dose-dependent manner. The order of agonist potency for this receptor was ATP = UTP > ATP-γ-S $\gg$ ADP. This ligand-selective profile indicates the expression of the $P2Y_2R$ subtype in these. RT-PCR using $P2Y_2$ primers amplified the expected transcript. The coupling of these receptors to phospholipase C was confirmed by the ability of ATP to increase $InsP_3$ production and to induce an early rise in $[Ca^{2+}]_i$ that was critically dependent on Ca^{2+} release. $P2Y_2R$ receptors expressed in cell lines are coupled to phospholipase D (PLD) pathway, leading to a sustained stimulation of phosphatidic acid and DAG production. Overexpression of PLD-1 in ovarian cells led to an increase in PEt accumulation, accompanied with attenuation in cell proliferation. Activation of $P2Y_2$ receptors by a slow degradable ATP-γ-S in native cells was associated with a time- and concentration-dependent attenuation in cell proliferation. To our knowledge $P2Y_2R$ subtype could be identified in human ovarian cancer tissue for the first time.

Conclusion: These human ovarian carcinoma cells express $P2Y_2R$, which are coupled to phospholipase C and phospholipase D pathway. Receptor and its coupling could possibly be a new target for cancer treatment.

912 POSTER DISCUSSION 1

Evaluation of the new polyclonal rabbit anti-human HER2/neu antibody – Overexpression of HER2/neu in ovarian cancer is associated with shortened overall survival

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Overexpression of the HER2/neu (c-erbB-2) cell-surface membrane receptor or the HER2 gene is detectable in 25–30% of breast cancers. This overexpression is an independent predictor of both relapse-free and overall survival in patients with breast cancer. For a number of malignancies an overexpression of HER2 and a correlation with worse prognosis has been reported, among these ovarian cancer. Testing for HER2 overexpression therefore could identify a subset of patients with a more aggressive tumour behaviour, that probably could benefit from a treatment with a monoclonal humanized antibody directed against the extracellular domain of the HER2 receptor (Herceptin, Trastuzumab; Genentech, USA). To get used with the antibody and to determine the percentage of HER2 overexpression in ovarian cancer we performed immunohistochemical staining of formalin-fixed, paraffin embedded tissue of ovarian cancers with the new FDA approved polyclonal rabbit anti-human antibody (DAKO, Glostrup, Denmark) with an automated staining system. The study population consisted of 38 patients with advanced ovarian cancers (pT3 and pT4 tumours), who received the same treatment regarding surgery and platinum consisting chemotherapy. The HER2 staining intensity and pattern was evaluted by two independent observers. Overexpression was recorded when a score of 2+ (weak to moderate staining in >10% of tumour cells) to 3+ (strong staining in >10% of tumour cells) out of a range from 0 to 3+ was detected. Cytoplasmic staining was considered as non-specific and was not included in further assessment. With respect to the small number of patients statistical calculations were not performed. Among the 38 ovarian cancers we observed overexpression of HER2 protein in 33.6% (15 of 38). These cases showed a remarkabely shortened overall survival (30.6 vs. 39.2 months). No difference was found

in the disease-free survival time (23.7 vs. 24.6 months). There was no trend of association with grading or tumour stage detectable. In conclusion we propose that testing of HER2 overexpression should be performed not only in breast but also in ovarian cancer. These patients should be considered for an additional treatment with Herceptin, but further investigation to confirm our results is needed.

913 POSTER DISCUSSION 1

Prognostic impact of tumor anemia in early-stage epithelial ovarian cancer

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Purpose: Tumor anemia is common in malignant tumors and adversely influences outcome of patients with various neoplasms. Pretreatment serum hemoglobin (Hb) was assessed to determine its effect on the survival of patients with epithelial ovarian cancer.

Methods: We conducted a retrospective, multicentric analysis based on the data of 553 patients with histologically proven epithelial ovarian cancer. Serum Hb levels were determined 24 to 48 hours before surgery and patients with serum Hb values below 12 g/dl were considered anemic. Data analysis included univariate and multiple Cox models.

Results: Tumor anemia was present in 143 (25.9%) patients before surgery. The overall survival probability was 33.6 and 47.0% in patients with pretreatment Hb levels <12 g/dl and >12 g/dl, respectively (Log rank p = 0.001). In a multivariate Cox model, pretreatment Hb values proved to be an independent prognostic factor for patients with FIGO state I–II epithelial ovarian cancer (n = 203), with survival probabilities of 61.2 and 73.7% in anemic and non-anemic patients, respectively. In contrast, pretreatment anemia failed to attain significance in patients with stage III–IV disease (n = 350).

Conclusion: Tumor anemia defined as pretreatment Hb values below 12 g/dl may indicate patients with early stage epithelial ovarian cancer, who are at increased risk of relapse.

914 POSTER DISCUSSION 1

'Reverse-schedule' topotecan and carboplatin in relapsed ovarian cancer: A phase I/II dose-ranging study

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Topotecan (TPT) is a topoisomerase 1 inhibitor which is active in relapsed ovarian cancer. There is a pharmacokinetic and pharmacodynamic interaction between TPT and both carboplatin [C] and cisplatin. When TPT is combined with platinum, the timing of platinum dosing with respect to TPT determines the maximum dose of TPT which can be administered. When C was given on day 1 with TPT on days 1 to 5, myelosuppression at the first dose level precluded further escalation (Simpson et al, 1998). In this reversed-schedule trial, patients (pts) with relapsed ovarian cancer received TPT on days 1–5 with C on day 5 after TPT, repeated every 21 days. C dose was calculated by the Calvert formula using EDTA clearance, and blood counts were monitored weekly. Doses of C and then TPT were escalated in successive cohorts; the first two dose levels are evaluable for toxicity. Four pts received 20 cycles of TPT 0.5 mg/m^2/day with C at AUC4, then C was escalated to AUC5 in the second cohort of 4 pts (16 cycles to date). There was no Grade 4 myelosuppression, and non-haematological toxicity was modest. Only 2 cycles were delayed, and no dose modifications were required. Formal assessment of response by CT scan is awaited, but the combination appears to be active with a significant fall in Ca125 in 5/8 patients. Accrual continues at the third dose level, TPT 0.75 mg/m^2/day with C at AUC5.

915 POSTER DISCUSSION 1

A phase II trial of concomitant brachytherapy and chemotherapy with docetaxel and cisplatinum combined with surgery and external radiotherapy for locally advanced uterine carcinoma

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Purpose: This study evaluated the feasibility, efficacy and toxicity of concurrent radio chemotherapy for locally advanced carcinoma of the cervix.

Material & Methods: 29 patients with various stages of cervical carcinoma of the uterus (7 St. IIA, 17 St. IIB, 5 St. IIIA) were treated from July 1996 untill December 1998. All patients received two Cs-137 Selectron MDR applications, 1 week apart. The dose calculated to point A for each implant was 25 Gy. Chemotherapy consisting of continuous docetaxel (50 mg m^{-2}) and cisplatin (50 mg m^{-2}) infusion, was given simultaneously with intracavitary, pelvic lymphadenectomy and pelvic radiotherapy.

Results: 24/29 patients were treated by wertheim hysterectomy of whom, 9 had negative lymph nodes and resection margins. Full dose external radiotherapy was given in the remaining 5 patients who were deemed ineligible for surgery, because of poor response. Overall, 25/29 (86%) were disease free at 19 months mean follow-up time. The most frequent acute side effects were nausea and vomiting. Leucopenia was seen in 3 patients and was responsible for delayed surgery in 2 cases. Concerning late effects, 3 patients developed grade 2 intestinal sequelae and one hemorrhagic cyctitis appeared in a patient suffering from sclerodermia.

Conclusion: Synchronous brachytherapy and chemotherapy with taxoids and platinum compounds is well tolerated and effective. It can cause downstaging of the tumour before definitive local treatment (surgery or external radiotherapy), in patients with locally advanced carcinoma of the cervix.

916 POSTER DISCUSSION 2*

Mortality from cervical cancer and endometrial cancer in East and West Germany from 1991 to 1997

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Purpose: Since 1991 the coding procedures for the death certificates according to ICD-9 are unified in East and West Germany (EG, WG). In order to monitor the trends of the mortality rates (MR) for cervical cancer (ICD9-180) (CxCa) and for malignancies of the uterus (ICD9-179 + 182) the development in both parts of Germany after the reunification was compared.

Methods: The raw data were provided by the Statistisches Bundesamt. Differences mortality between EG and WG were analysed, of the age-standardized rates (aMR) calculated in 5-year age groups (MR) and compared.

Results: From 1991 to 1997 a constant decrease of the aMR of CxCa can be observed in EG and WG. The aMR EnCa are decreasing until 1995 and remain stable until 1997. The aMR are higher in EG than in WG for the whole period; the trends are similar in WG and in EG. For CxCa no significant differences of the MR can be seen in different age groups between 1991 and 1997; for EnCa a decrease of the MR in the over 75 years old in 1991 cannot be found in 1997. The median age of death compared between 1991 and 1996 has been nearly unchanged (CxCa: 1991: 64.6 y; 1996: 65.3 y; EnCa: 1991: 73.5 y; 1996: 73.3 y).

Conclusion: The aMR of CxCa is decreasing from 1991 to 1997 while the decrease of the aMR of EnCa ends in 1995. Mortality of EnCa and CxCa is consistently higher in EG. No 5-year age group can be identified, that shows significant differences in the MR in 1997 compared to 1991. The underlying reasons for the differences of MR will be analysed in future studies.

917 POSTER DISCUSSION 2*

Combined chemo-radiotherapy for locally advanced cancer of the cervix: A review of randomized clinical trials

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Purposes: To investigate the role of chemotherapy added to radiotherapy for locally advanced cancer of the cervix.

* Poster Discussion 2 will be held on Thursday 16 September 1999