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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)

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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