1204 POSTER

Treosulfan vs. leuprorelin in platin- and paclitaxel-resistant ovarian cancer: final analysis of the german ago-study group trial ovar 2.1

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Objective: We report about the first prospective randomized trial comparing endocrine treatment with GnRH analoga and chemotherapy with treosulfan in early progressive ovarian cancer.

Methods: The study comprised 73 evaluable patients who were equally randomized for therapy either with treosulfan 7g/m2 i.v., day 1/q 28 days (arm A) or with leuprorelin 3.75 mg s.c., day 1/q 28 days (arm B) Evaluation was performed considering remission, survival time, toxicity and particularly quality of life.

Results: No objective responses could be observed. The median survival time was 36 wks. and 30 wks in the Treosulfan- and Leuprorelin-arm, respectively. The median time to progression was 17 wks. in arm A and 10 wks in arm B, which was not significantly different. 20% of patients receiving chemotherapy showed stable disease compared with 11% in the GnRH group. Both arms demonstrated low rates of grade 3/4 hematologic toxicity without accurence of any febrile neutropenia. Alopecia was seen in 15% of patients (arm A) and 5% (arm B), respectively.

Conclusion: In the group with early relapse of ovarian cancer, who has the worst prognosis at all, the final analysis showed no difference between chemotherapy with an alkylating agent and leuprorelin, although there was a tendency towards chemotherapy.

1205 POSTER

Cisplatin/Paclitaxel vs. Carboplatin/Paclitaxel in 798 patients with ovarian cancer FIGO IIB-IV - Randomized phase III study the AGO (Arbeitsgemeinschaft Gynaekologische Onkologie) Study Group (OVAR-3 trial)

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Objective: Evaluation of the efficacy, toxicity and quality of life in ovarian cancer patients treated with either cisplatin/paclitaxel or carboplatin/paclitaxel as first-line treatment.

Methods: 798 pts. were recruited in a randomized trial comparing carboplatin AUC 6 + paclitaxel 185 mg/m* 3 hrs iv q21 (arm A) with cisplatin 75 mg/m* + paclitaxel 185 mg/m* 3 hrs q21 as first-line chemotherapy for ovarian cancer patients IIB-IV. Primary endpoint was progression free survival (PFS).

Results: After median follow-up of 100 wks. 392 pts. in arm A and 385 pts. in arm B were evaluated. Median PFS were 76 and 72 wks in arm A and B, respectively (hazard ratio 1.07 with 90% confidence interval 0.91 - 1.25. p=0.54). Overall survival after 2 years did not differ between both treatment arms (p=0.27). Response evaluation was done in 83 pts. in arm A and 70 pts. in arm B who had measurable disease. Complete and partial responses were observed in 75.9 and 80% in arm A and B, respectively (p=0.11). Hematological toxicity occurred more frequently in arm A. Quality of life during treatment was significantly inferior in arm B.

Conclusions: Both treatment arms showed equivalent efficacy, but carboplatin/paclitaxel had a superior therapeutic index due to better tolerance as measured by toxicity and quality of life analysis.

1206 POSTER

ATF-HI8, a chimeric molecule of bikunin, suppresses migration and invasion in ovarian cancer cells

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Purpose: It has been reported that bikunin, a urinary trypsin inhibitor, has an inhibitory activity against cancer metastasis and invasion. A chimeric molecule, derived from HI8(the active site of bikunin) and an amino terminal fragment (ATF: uPA receptor binding site), have been developed to increase the affinity for the cancer cell surface. In this study, we examined the actions of the chimeric gene against cancer metastasis and invasion. Methods: We isolated ATF and HI8 genes from the placenta-derived uPA cDNA and bikunin cDNA, respectively, by PCR cloning, and constructed a plasmid expressing chimeric ATF-HI8. ATF-HI8 gene was transferred into the human ovarian cancer cell line HRA by the standard calcium phosphate precipitation method. ATF-HI8 transfectant of HRA (HRA-ATF- HI8) and the control (HRA-luciferase (LUC)) cells were plated in 6-well plate by 50,000 cells/well and cultured in 10% serum-supplemented DMEM. After 24, 48, 72, and 96 hours, the cells were dislodged and counted by a hemocytometer. Cell migration was measured by the in vitro scratch wound healing assay. Monolayer cells were scratched with a sterile pipette tip in 10 cm plastic dishes, and after 8 hours of culture in 2% serum-supplemented DMEM, cell migration was evaluated by counting cells that migrated from the wound edge. Cell invasion was measured by using a matrigel-coated chamber. Cell suspension (200,000 cells in 500ul) was placed in the upper compartment of the chamber. The chambers were incubated for 20 hours. At the end of the incubation, the cells on the lower surface of the membrane were stained and counted under a light microscope. Results: There was no difference in cell growth between HRA-ATF-HI8 and HRA-LUC. The number of HRA-ATF-HI8 migrated to the scratched area was 204±70 cells, which was significantly smaller than those of HRA-LUC (363±134 cells) ($P<0.05$). The number of HRA-ATF-HI8 invaded to the lower surface of the membrane was 102±28 cells, which was significantly smaller than those of control (354 ±26 cells) ($P<0.001$). Conclusion: We constructed an ATF-HI8 expressing plasmid vector that can be expressed in a human cell line. We found that ATF-HI8 gene suppressed migration and invasion of ovarian cancer cells. A viral vector mediated delivery of this chimeric gene ATF-HI8 carries prospects for future applications to gene therapy for ovarian cancer.

1207 POSTER

Expression of Interleukin-10 Inhibits angiogenesis and tumor growth in ovarian cancer

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Purpose: Interleukin-10 (IL-10) is an immunosuppressive cytokine produced by T lymphocytes, and has recently been drawing attention as an inhibitor of tumor angiogenesis. In this study, we investigated anti-angiogenic and tumor-suppressive effects of IL-10 in ovarian cancer cells. Methods: Murine IL-10-expressing plasmid was constructed and transferred to two ovarian cancer cell lines, SHIN-3 (VEGF-producing) and KOC-2S (non-VEGF-producing) cells by calcium phosphate-mediated transfection. After selection, mIL-10-expressing cells were obtained and named as SHIN-3/mIL-10 and KOC-2S/mIL-10, respectively. Expression of mIL-10 was determined by western blot analysis of culture supernatants. Cell proliferation was examined for up to 7 days. The angiogenic activities of mIL-10-expressing cells were measured by dorsal air sac assay, which detected the number of newly formed blood vessel within a chamber in vivo. Tumor formation was evaluated by subcutaneous tumor transplantation, and survival was monitored following intraperitoneal injection of ovarian cancer cells in BALB/c nude mice. Results: Western blot analysis of culture supernatants showed mIL-10 expression specific for transfected cells. No significant differences were observed in growth properties between the mIL-10-expressing cells and the control (luciferase-expressing cells) in both KOC-2S and SHIN-3. In vivo angiogenic activity and tumor growth were significantly inhibited in SHIN-3/mIL-10 cells compared with the control ($p<0.05$). Also, peritoneal dissemination was inhibited and the survival period was significantly prolonged (mean survival days>90 versus 36, $p<0.05$). In contrast, in KOC-2S cells, no significant differences were observed in the angiogenic activity, tumor growth, peritoneal dissemination, or survival time between KOC-2S/mIL-10 cells and the control. Conclusion: IL-10 exhibited suppressive effects on angiogenesis, tumor growth, and peritoneal dissemination of VEGF-producing ovarian cancer cells. Although the precise mechanism of action is yet to be determined, anti-angiogenic effect of IL-10 might be associated with downregulation of VEGF expression and/or inhibition of intracellular VEGF signaling pathway.