IS-28 Phase II study of relative high dose topotecan plus carboplatin in the treatment of patients with recurrent epithelial ovarian cance

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Objective: The aim of this study was to investigate the toxicity profile and therapeutic efficacy of a novel high dose combination regimen, topotecan plus carboplatin, at first or second relapsed epithelial ovarian cancer. Methods: 53 patients with recurrent epithelial ovarian cancer after platinum-based chemotherapy were entered onto this study and received topotecan plus carboplatin at the Samsung Medical Center between March 2003 and December 2007. Topotecan was given at an initial dose of 1 mg/m2 daily (days 1-5), combined with carboplatin at a dose of AUC 5 (Calvert formula) on days 5. Toxicity was assessed before every cycle according to the WHO Toxicity Criteria. The primary efficacy parameters were response rate (RR), duration of response, time to progression (TTP) and overall survival. Responses were determined according to the RECIST criteria. Results: Median age was 51 years (range 30-77 years). The majority of patients had a performance status of 0 to 1. 233 courses of the chemotherapy were administered to 53 patients (25 patients who received one prior regimen and 28 patients who received two prior regimens). The median dose-intensity of topotecan for all patients was 1.49 mg/m2 weekly, close to the target dose of 1.67 mg/m2 weekly. Grade 3/4 neutropenia was experienced in 50.7% of the treatment courses. Treatment with G-CSF was administered in 30.5% of the courses. Grade 3/4 thrombocytopenia was observed in 30.5% of the courses and required platelet transfusions in 28% of the courses. Thrombocytopenia was associated with a serious bleeding event in two patients in the first and second cycle, respectively. Grades 3/4 anemia was experienced in 19.8% of the treatment courses with RBC transfusions in 56.2% of the courses. There was no evidence of cumulative toxicity. There were seven episodes of febrile neutropenia, but all episodes could be managed successfully with supportive care. No deaths occurred caused by sepsis. And nonhematologic toxicities were generally mild. A RR of 26.4% (14 of 53 patients) was found which consisted of 9 PRs and 5 CRs. Higher response rates were seen in patients who were platinum sensitive compared with those platinum resistant (40.0% v 8.7%; P=0.010) and in patients who had ≥6months TFI compared with those<6months (42.3% v 11.1%; P=0.010). Response duration was 7momths (95CI, 5.17-8.83), TTP was 6months (95CI, 4.22-7.78), and overall median survival was 19months (95 CI, 13.4-23.7). Conclusions: Topotecan combined with carboplatin has a acceptable toxicity profile and considerable response rate in patients with recurrent ovarian cancer after platinum-based chemotherapy.

IS-29 The role of FOXO1 in the mechanism of cytotoxicity and drug-resistance induced by paclitaxel in ovarian cancer

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[Objective] Drug-resistance is the major problem for treatment against ovarian cancer patients. Since transcriptional factor FOXO were reported to be critical mediators of apoptosis in cytotoxicity inducing drugs in many cells, we investigated the role of FOXO1 in the mechanism of cytotoxicity and drug-resistance in ovarian cancer. [Methods] In ovarian cancer cell lines, using parent cell line KF28, cisplatin resistant derivative cell line KFr13 and paclitaxel resistant derivative cell line KFr13Tx, FOXO1 expression and its correlation with paclitaxel treatment was investigated by cytotoxic assay and silencing experiment. [Results] FOXO1 expression was distinctively upregulated in paclitaxel resistant cell line, and enhanced by exposure to paclitaxel. FOXO1 silencing in paclitaxel resistant cell line decreased its resistance. Modification of oxidative stress by co-treatment with pharmacologic modulators of reactive oxygen species pathway attenuated cytotoxicity of paclitaxel in ovarian cancer cells, suggesting involvement of FOXO1 in altered sensitivity to paclitaxel through its downstream target. [Conclusion] These results indicate that FOXO1 links to cytotoxicic stress induced by paclitaxel and contributes to the drug-resistance in ovarian cancer cells.

IS-30 Usefulness of third-line chemotherapy for women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who receive platinum/taxane regimens as first-line therapy

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[Objective] The aim of this study was to investigate the predictors of the response to third-line chemotherapy with recurrent ovarian, fallopian tube, and primary peritoneal cancer (ROFTPPC) who received platinum/taxane (PT) regimens as first-line therapy. [Methods] We retrospectively reviewed the medical records of ROFTPPC that were treated between 1999 and 2005 to investigate the relations of clinicopathological factors to important clinical endpoints such as the response rate (RR), time to progression (TTP) and overall survival (OS) after third-line chemotherapy. [Results] A total of 172 patients received first-line PT regimens during the study period, among whom 111 had disease progression after first-line chemotherapy. Eighty-one of these 111 patients received second-line chemotherapy, and 73 had disease progression. Fifty-four of the 73 patients with disease progression received third-line chemotherapy. The RR to third-line chemotherapy was 40.7%. The median TTP was 4.4 months, and the median OS was 10.4 months. Performance status (PS) and primary drug-free interval (DFI) were independent predictive factors for the RR, TTP and OS. [Conclusion] PS and primary DFI are useful predictors of the response to third-line chemotherapy in women with ROFTPPC. In this setting, however, both of these variables are subject to several well-established potential biases and limitations.