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The effect of anemia on the progression-free survival in epithelial ovarian cancer (stage II-IV) patients treated with paclitaxel-carboplatin combination therapy: a retrospective analysis of the JGOG3016 trial of the Japanese Gynecologic Oncology Group (JGOG3016-A)

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Background: We conducted the randomized phase III study of conventional paclitaxel-carboplatin combination therapy (c-TC) and weekly dose dense TC (dd-TC), and the advantage of dd-TC on PFS was reported at the 2008 ASCO Annual Meeting (JGOG3016). We investigated the effect of anemia on PFS, with focus attention on “anemia”, which was frequently observed in the dd-TC group as the major adverse event.
Methods: Among the patients who were enrolled in JGOG3016 and treated at least one cycle or more, the development of anemia before and after the treatment was retrospectively investigated. A patient with 8 g/dL of hemoglobin (Hb) or less (Grade 3 or more: CTCAE) was classified into the anemia group and background factors affecting the development of anemia were investigated. Furthermore, the anemia and non-anemia groups were matched by Caliper method, and the effect of anemia developing after the beginning of treatment on PFS was investigated after the background factors of “weight”, “age”, “PS” and “residual tumor” were adjusted. The patients “histological type”, “stage” and “surgical history” were also adjusted in the background factors.
Results: Total 622 patients (c-TC group: 314, dd-TC group: 308) were investigated and anemia of Grade 2 or more was found in 123 (19.8%) patients before the treatment. Anemia of Grade 3 or more was observed in 137 (43.6%) patients of the c-TC group and 211 (68.5%) patients of the dd-TC group after the treatment. In comparison after adjusting background factors by matching, the median PFS was 519 days in the anemia group (Grade 3 or more after the treatment) and 460 days in the non-anemia group of the c-TC group ($p = 0.5513$), on the other hand, 777 days in the anemia group and 1,100 days in the non-anemia group of the dd-TC group ($p = 0.3493$).
Conclusions: The results of this study showed the actual condition of anemia in ovarian cancer patients treated with standard TC therapy, and suggested the possibility that the development of anemia affected PFS. In particular, weekly dd-TC therapy is expected to further improve the outcomes when the anemia is corrected. A prospective study should be performed to investigate whether PFS is substantially improved by preventing severe anemia with ESAs.

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Prognostic factors and survival analysis in pre- and postmenopausal patients with epithelial ovarian cancer

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Background: Prognostic factors for epithelial ovarian cancer may differ between pre- and postmenopausal pateints. To discuss the difference, authors conducted a retrospective analysis to elucidate the impact of clinic pathological factors, cytokines, CA125 and immunological status on survival in pre- and postmenopausal epithelial ovarian cancer.
Material and Methods: The study included 55 pre-menopausal and 55 postmenopausal patients with epithelial ovarian cancer treated with cytoreductive surgery followed by platinum-based chemotherapy in Zhejiang Cancer Hospital from 2003 to 2005. Flow cytometry was employed to detect serum cytokines, IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-10 and lymphocyte subset, CD3, CD4, CD8, CD19, CD25, CD56, CD44, for evaluating immunological status. Micropartical enzyme immunoassay was used to measure serum CA125. Pearson chi test was used in univariate analyses and a multivariable proportional hazard model was applied to assess the prognostic significance of the different covariates.
Results: No significant difference of clinicopathological factors, serum cytokines, immunological status and serum CA125 was found between pre-menopausal and postmenopausal women with epithelial ovarian cancer. However, 3-year overall survival rate in postmenopausal women with epithelial ovarian cancer was less than that in premenopausal patients(29% vs 56%, $P < 0.01$). Bilateral ovarian cancer and high CA125 level were significantly associated with worse overall survival compared to one side ovarian cancer and low CA125 level in both pre- and postmenopausal patients. Additionally, menarcheal age, abortion times, tumor stage, CD4, CD8, CD56, CD25, CD44 levels were significantly correlated to overall survival of pre-menopausal women with ovarian cancer.
Conclusions: Bilateral ovarian cancer and high CA125 level are independent unfavorable prognostic factors in both pre- and postmenopausal patients with ovarian cancer. Immunological status may affect overall survival of pre-menopausal patients with ovarian cancer.

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Platinum-sensitive relapsed epithelial ovarian cancer: how much does the treatment-free interval matter?

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Background: While platinum resistant/refractory ovarian cancer generally exert an extensive chemoresistance containing almost against all available cytostatic agents, platinum containing regimens can be readministered to patients with platinum-sensitive disease, with different efficacy mainly depending on the interval from the end of previous platinum-based chemotherapy (TFI).
Patients and Methods: Patients with measurable, platinum-sensitive recurrent epithelial ovarian carcinoma were eligible. Platinum sensitivity was defined as follows: patients with disease that relapsed 6−12 months after completion of a platinum-based regimen were considered partially platinum-sensitive, and those patients who relapsed after 12 months from the end of a previous regimen were considered pure platinum-sensitive patients. All patients FIGO IIB-IV were primarily treated with cytoreductive surgery followed by paclitaxel-carboplatin chemotherapy and the same chemotherapy regimen was applied as second-line treatment after disease reccured. RECIST criteria and CTCAE V3.0 were used to monitor therapy response and toxicity.
Results: Overall thirty-nine patients were evaluated for efficacy and toxicity, out of which 36% had partially and 64% pure sensitive relapsed ovarian cancer. Fifteen (38%) patients had a complete response, seven (18%) had a partial response, one (3%) had stable disease and sixteen (41%) experienced progressive disease. Overall RR (ORR) was 12.8% in partially platinum-sensitive disease and 44% in pure platinum-sensitive disease, indicating a tendency for better ORR with readministration of the same chemotherapy regimen in the pure platinum-sensitive in comparison with partially platinum-sensitive group; $p = 0.051$, chi-squared test. No statistically significant difference was observed between partially and pure platinum-sensitive patients regarding median TTP (20 vs. 17 months respectively; $P = 0.508$). Four patients experienced G4 leukoneutropenia, and 4 patients had G2 peripheral neuropathy.
Conclusion: Our results, in terms of ORR support the use of the same platinum-based regimen only in those patients relapsing after 12 months from the end of previously delivered platinum chemotherapy regimen. Thus, these data clearly indicate that appropriate selecton of chemotherapy regimen in treatment of relapsed ovarian cancer predominantly depends of response duration on primary treatment.

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Comparison of tumour size and metastases in stage I and III primary epithelial ovarian cancer

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Background: Two small studies have found larger primary ovarian carcinomas in stage I as compared to stage III disease. Thus, these stages may represent different entities.
Methods: We retrospectively analyzed the charts from 553 patients (stage I: $n = 177$; stage III: $n = 376$) operated on at the Dept. OB/GYN of the Medical University of Graz between 1980 and 2008 because of epithelial ovarian cancer. Macroscopic, microscopic histopathological and surgical reports were analyzed.
Results: Primary lesions were significantly larger in stage I disease as compared to stage III disease. No such association was found when invasive components only were analyzed. The size of the invasive primary tumor was not associated with the largest size of the intraperitoneal metastasis. The invasive tumour size of the primary was neither predictive for survival in stage I nor in stage III disease, respectively. Larger metastases were associated with ascites, bowel involvement, tumour residuals > 2 cm and an inferior prognosis. Lymphadenectomy was more prevalent in cases with smaller intraperitoneal metastases.

Conclusions: In FIGO stage I disease, primary lesions including benign, borderline and invasive components were significantly larger than those in stage III disease. However, no such correlation was found when only the invasive tumour components were analyzed. The invasive primary tumour size did not influence survival in either stage I or III disease. There was no correlation between the size of the primary invasive tumour and the size of intraperitoneal metastases. Larger metastases were associated with the presence of ascites, bowel involvement, tumour residuals > 2 cm and a shorter progression-free and overall survival.

8025 POSTER

Correlation of Topo II alpha expression and amplification with efficacy of pegylated liposomal doxorubicin in a GEICO phase II trial for platinum-resistant (PR) recurrent ovarian carcinoma (ROC)

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Background: Topo IIa is an enzyme which plays a critical role in DNA replication and recombination, and is also the target for doxorubicin. Response to doxorubicin has been associated to Topo IIa in breast cancer.
Materials and Methods: Tissue samples from patients participating in a prospective phase II trial with pegylated liposomal doxorubicin in platinum-resistant ROC conducted by GEICO were obtained for the analysis (Casado A et al. ASCO 2003. Abstract 1942). Topo IIa expression was determined by inmunohistochemistry (IHC) and amplification by fluorescence in situ hybridization (FISH). Topo IIa was considered positive with $\geqslant$ 10% cells stained by IHC.
Results: Samples from 45 patients of the 82 included in the trial were obtained and valid for the analysis. The rate of expression by IHC was: 0% (20%), <10% (35.5%), $\geqslant$ 10% (44.4%). Only 1 patient had amplification. The response rate obtained in 44 evaluable patients was: 1 CR (2.2%), 3 PR (6.8%), SD (31.8%). No response was observed in patients without expression of Topo IIa. The 3 patients with PR were seen in the group with an IHC staining $\geqslant$ 10%, and the patient with CR was in the group with IHC staining <10%. The patient with CR was also the only one with amplification observed in our study. The rate of SD was similar in the 3 groups independently of the expression by IHC. Correlation between Topo IIa expression and progression free survival will be presented.
Conclusions: Topo IIa expression and amplification may be a predictor of response to pegylated liposomal doxorubicin in patients with platinum-resistant ROC. Further studies confirming this hypothesis are warranted.

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The predictive and prognostic value of serum CA125 kinetics and CA125 nadir during paclitaxel/platinum based chemotherapy (QT) in patients with advanced ovarian carcinoma (OC)

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Background: The tumor marker CA125 is an accurate and reliable marker for monitoring the response and detecting early relapse in OC. The aim of this retrospective study is to analyze the predictive and prognostic value of CA125 kinetics and the implications of the different levels of CA125 within the normal range after QT.
Methods: Over a 13 years (1996−2008), 127 patients (pts) were treated with standard QT regimen for FIGO stage IIb-IV epithelial OC. The median age was 64 years old (range, 24−87 years). The tumors were classified: 70(55%) serous, 24(19%) poorly differentiated, 14(11%) endometrioid and 19(15%) clear cell carcinoma. FIGO stage: 12(9%) II, 95(75%) III and 20(16%) IV. Tumor grade: 1(1%) G1, 11(9%) G2 and 115(90%) G3. Residual disease after initial surgery: 52(41%) <2 cm and 39(31%) >2 cm. After surgery 117(92%) of the pts received a median of 6 cycles with platinum based (cisplatin or carboplatin) QT in combination with paclitaxel. Serial measurement of CA125 had been made before each cycle of QT. Median follow-up has been 31months. Ninety-three(73%) pts achieved levels <35U/ml after completion of QT. The nadir value of CA125 was stratified into three arbitrary groups: group 1, $\leqslant$10 U/ml, group 2, 11−20 U/ml and group 3, 21−35 U/ml. The pre-QT CA125 level was categorized into two arbitrary groups: group A $\leqslant$200 U/ml and group B>200 U/ml. Time to nadir and time to negativization were also studied and classified into two arbitrary groups: group A$\leqslant$72 days and group B>72 days. CA125 half-life was calculated by mono-compartmental logarithmic regression. Survival analyses for disease-free survival (DFS) and overall survival (OS) used univariate (Kaplan-Meier) and multivariate (Cox) model.
Results: For 127 pts, 88(69%) relapsed and 60(47%) died. DFS according to 3 groups was 34, 20, 14 months, respectively ($p < 0.0001$). OS for groups 1, 2 and 3 was 7.5, 3 and 3 years, respectively ($p < 0.0001$). Pre-QT CA125 ($p < 0.002$) and time to negativization ($p < 0.043$) all had a univariate prognostic value for DFS and OS. In Cox models, FIGO stage ($p < 0.0001$) and nadir concentration ($p < 0.0001$) were the most powerful prognostic factors for DFS and OS. We found no differences in DFS and OS related to time to nadir and CA125 half-life.
Conclusion: Serum CA125 kinetics during early QT has a strong predictive and prognostic relevance for pts with advanced OC. Besides, within normal range, the differences between CA125 levels could add prognostic information and stratify pts according to the risk of progression. Categorizing pts would be a useful tool when performing consolidation QT in future clinical trials.

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18FDG PET staging versus conventional (CT scan and laparoscopy) staging in advanced epithelial ovarian cancer: correlation with survival

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Background: Epithelial ovarian cancer (EOC) is diagnosed in advanced stages in up to 70% of cases; chest and abdomen CT scan and open laparoscopy (conventional staging) are usually performed in order to evaluate the optimal therapeutic approach (upfront debulking surgery versus primary chemotherapy). The use of ^{18} FDG-PET has been proposed in order to assess the response to neoadjuvant chemotherapy but its role in the initial staging EOC is unclear. The aim of this study (a part of the Arianna 02 Project) is to compare the conventional staging with the PET staging in patients candidate to neoadjuvant chemotherapy for advanced EOC.
Material and Methods: Eligible pts had stage IIIC-IV EOC unsuitable for optimal upfront surgery according to standard CT scan and open laparoscopy evaluation. Six courses of neoadjuvant carboplatin AUC 5 and paclitaxel 175 mg/sm, every 3 weeks were administered before surgery. ^{18}FDG-PET was performed at baseline in order to compare the PET staging with the conventional staging (as defined above). Survival according to stage was analyzed with Kaplan-Meier analysis.
Results: 48 stage III/IV pts were enrolled and received neo-adjuvant chemotherapy. In 38 pts PET and conventional staging were in accordance (23 stage III and 15 stage IV), while 6 stage IV and 4 stage III pts by conventional staging were classified as stage III and stage IV by PET, respectively (overall concordance 80%). After a median follow-up of 29 mo.s, 36 pts (75%) have progressed, and 26 (54%) have died. When staged by conventional method the median time to progression and overall survival for stage IIIC vs stage IV patients were 15 vs 11 mo.s ($p = 0.22$) and 34 vs 20 mo.s, respectively ($p = 0.27$).
On the contrary, when PET stage was considered, median TTP (20 vs 8 mo.s, p 0.001) and OS (43 vs 18 mo.s, $p = 0.001$) were significantly longer for stage III vs stage IV pts.
Conclusion: initial staging of advanced EOC patients by ^{18} FDG-PET correlates with baseline prognosis in patients unsuitable for upfront surgery and treated with neoadjuvant chemotherapy.