symposium article

Dose-dense therapy is of benefit in primary treatment of ovarian cancer? In favor

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Paclitaxel and carboplatin given every 3 weeks is the current standard treatment in first-line chemotherapy regimens for ovarian cancer. The concept of ‘dose-dense therapy’ is based on the hypothesis that a shortening interval of the doses of cytotoxic agents will be more effective for tumor-cell kill. Recently published phase III trials in breast cancer have shown that dose-dense weekly paclitaxel improves response and survival. The Japanese Gynecologic Oncology Group reported a phase III study comparing the conventional 3-weekly paclitaxel and carboplatin schedule versus dose-dense weekly paclitaxel and 3-weekly carboplatin for advanced epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer. The progression-free survival, as the primary endpoint of this study, was significantly prolonged with the dose-dense treatment (28 months versus 17.2 months; hazard ratio (HR): 0.71; 95% confidence interval (CI): 0.58–0.88; P = 0.0015), as was the overall survival at 3 years (72.1% versus 65.1%; HR 0.75; 95% CI: 0.57–0.98; P = 0.03). Dose-dense weekly paclitaxel plus carboplatin represents a new treatment option in women with advanced epithelial ovarian cancer.

Key words: advanced epithelial ovarian cancer, dose-dense therapy, paclitaxel

Introduction
Currently, the combination of paclitaxel and carboplatin (TC) is the standard first-line chemotherapy for ovarian cancer. In its most recent consensus statements on the management of ovarian cancer during the Fourth International Ovarian Cancer Consensus Conference, the Gynecologic Cancer InterGroup (GCIG) confirmed this. GCIG recommended the use of 175 mg/m² paclitaxel, given intravenously (i.v.) over 3 h, followed by carboplatin as an i.v. infusion over 30–60 min at a dose adjusted to produce an area under the plasma concentration–time curve (AUC) of 5–6 mg l/min to and repeat this every 3 weeks for six cycles [1]. Moreover, GCIG considered intraperitoneal therapy in patients with small-volume residual disease and dose-dense weekly paclitaxel in combination with 3-weekly carboplatin acceptable treatment options.

The concept of dose-dense therapy
‘Dose-dense therapy’ is a strategy to enhance antitumor activity and prolong the survival of patients. The theoretical basis for this dose-dense chemotherapy strategy is derived from the Gompertzian model, which is based on Norton–Simon’s hypothesis [2, 3]. In the Gompertzian model, smaller tumors grow faster and so tumor regrowth between treatment cycles is more rapid when cell kill is greatest. Increased dose density is achieved by reducing the interval between each dose of chemotherapy. The cumulative drug dose remains constant, but the same amount of drug is administered over a shorter period. Mathematical models of tumor growth have provided the basis for the clinical application of dose-dense chemotherapy. The Norton–Simon model suggests that increasing the dose density of chemotherapy will increase efficacy by minimizing the opportunity for regrowth of tumor cells between cycles of chemotherapy. This concept has been applied in adjuvant therapy, in sequential administration of chemotherapy and in dose-dense administration of chemotherapy, in particular for breast cancer. The Cancer and Leukemia Group B C9344 study demonstrated that the sequential use of paclitaxel following doxorubicin and cyclophosphamide as adjuvant therapy for breast cancer improved survival [4]. Weekly paclitaxel as compared with every-3-weeks administration of paclitaxel improved survival in two phase III trials of breast cancer [5, 6]. A meta-analysis of dose-dense chemotherapy in non-metastatic breast cancer demonstrated a better overall and disease-free survival [7].

dose-dense paclitaxel for ovarian cancer

The weekly administration of paclitaxel has been investigated from preclinical studies to clinical trials. The results from some in vitro studies indicate that increasing the number of short paclitaxel infusions results in a greater response rate than the normal 24-h administration period [8]. Preclinical studies have suggested that the duration of exposure is an important determinant of the cytotoxic activity of paclitaxel [9]. Adequate cytotoxicity can be achieved at relatively low concentrations of paclitaxel, provided that the exposure is prolonged [9, 10]. It
has also been suggested that in addition to its microtubule-stabilizing action, paclitaxel may have other cytotoxic effects, such as inducing apoptosis and inhibiting angiogenesis, which are even observed at very low concentration levels of paclitaxel and even under weekly administration [11].

A phase I study conducted at the Memorial Sloan Kettering Cancer Center by Leser et al. [12], included 16 relapsed ovarian cancer patients. Weekly paclitaxel escalating dose of 50–80 mg/m² and carboplatin AUC 4–6 every 3 weeks were administered. Febrile neutropenia and grade 4 thrombocytopenia according to the National Cancer Institute common toxicity criteria were the dose-limiting toxicities at dose levels 3 and 4 with no mucositis, nausea, vomiting or peripheral neuropathy observed greater than grade 2. They recommended weekly paclitaxel 80 mg/m² in combination with carboplatin AUC 5 every 3 weeks for further study. Kikuchi et al. [13] conducting a similar phase I trial, in Japanese patients with advanced non-small cell lung cancer, recommend a dose of weekly paclitaxel 100 mg/m² on days 1, 8, and 15 in combination with carboplatin AUC 6 every 4 weeks.

Several phase II clinical trials of dose-dense weekly paclitaxel and carboplatin administration have shown promising efficacy and favorable tolerability in women with ovarian cancer [14–16]. We reported a phase II study of 80 mg/m²² paclitaxel and carboplatin AUC 2, which were administered every week in recurrent ovarian cancer patients [14]. The objective response rate was 67% (22/33). Grade 3–4 leukopenia was observed in 25% of patients and grade 3–4 neutropenia in 57% of patients. However, no patient was given granulocyte-colony stimulating factor. Febrile neutropenia was not observed. Grade 3 neurotoxicity was observed in 4% of patients. All patients were treated in the outpatient clinic. In another study, Sehouli et al. [16] reported weekly administration of 100 mg/m²² paclitaxel and weekly carboplatin AUC 2, and showed substantial activity and tolerability of this regimen when treating patients in the primary disease setting. A treatment delay of only 2.8% was observed and the incidence of grade 3 neurotoxicity was even lower than that in our study. In addition, Pignata et al. reported that weekly carboplatin at a dose of AUC 2 and weekly paclitaxel at a dose of 60 mg/m²² on days 1, 8 and 15, every 4 weeks, had a favorable toxicity profile in elderly ovarian cancer patients, when treated in first line [17].

**randomized phase III trial of dose-dense weekly paclitaxel in combination with carboplatin for advanced ovarian cancer**

The Japanese Gynecologic Oncology Group (JGOG) conducted a randomized phase III trial of dose-dense weekly paclitaxel in combination with 3-weekly carboplatin for advanced ovarian cancer [JGOG 3016; New Ovarian Elaborate (NOVEL) trial] [18].

Patients with stage II–IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer were randomly assigned to receive six cycles of either paclitaxel plus carboplatin, given on day 1 of a 21-day cycle [conventional TC (c-TC)] or dose-dense paclitaxel, given on days 1, 8 and 15, plus carboplatin given on day 1 of a 21-day cycle [dose-dense TC (dd-TG)]. Both groups received carboplatin at a dose calculated to produce an AUC of 6 mg/ml/min on day 1 of each 21-day cycle. Carboplatin was given as an i.v. infusion over 1 h. The conventional therapy group received paclitaxel given as a 3 h i.v. infusion at a dose of 180 mg/m² body surface area on day 1. In the dose-dense therapy group, paclitaxel was given as a 1 h i.v. infusion at a dose of 80 mg/m² body surface area on days 1, 8 and 15. The dose of carboplatin was calculated with the Calvert formula [19], using the creatinine clearance instead of the glomerular filtration rate (GFR). The creatinine clearance was calculated with the Jelliffe formula [20]. The treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or a complete response received three additional cycles of chemotherapy. The primary endpoint was progression-free survival. Secondary endpoints were overall survival, response rate and adverse

![Figure 1. Progression-free and Overall Survival.](image-url)
In conclusion, dose-dense TC is an effective treatment with improved progression-free survival in patients with advanced ovarian cancer. Confirmatory studies are ongoing in Western countries. GOG 262 (trial registration: NCT01167712; Figure 2) is comparing carboplatin AUC 6 plus 175 mg/m² paclitaxel given every 3 weeks with carboplatin AUC 6 plus weekly 80 mg/m² paclitaxel given every 3 weeks for suboptimal stage III or IV ovarian cancer. Additional bevacizumab is an option in the study. MITO 7 (trial registration: NCT00660842; Figure 3) is comparing carboplatin AUC 5 plus 175 mg/m² paclitaxel with weekly carboplatin AUC 2 plus weekly 60 mg/m² paclitaxel. ICON 8 is preparing to start a three-armed randomized trial comparing carboplatin AUC 5 plus 175 mg/m² paclitaxel with carboplatin AUC 5 plus weekly 80 mg/m² paclitaxel and with weekly carboplatin AUC 1.67 plus weekly 80 mg/m² paclitaxel for stage IC to IV ovarian cancer. It is reasonable to conclude that if these studies confirm the Japanese phase III trial data, then weekly paclitaxel administration is an appropriate strategy to consider in the standard treatment of advanced ovarian cancer.

**GOG262**

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<td>Carboplatin AUC 6</td>
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<td>Paclitaxel 175 mg/m²</td>
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<td>q3 wks</td>
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**Arm II**

| Carboplatin AUC 6 |
| Paclitaxel 80 mg/m² |
| q3 wks |
| 6 cycles |

Optional* bevacizumab 15 mg/kg IV Day 1 beginning with cycle 2 Every 21 Days x 6 followed by maintenance bevacizumab 15 mg/kg IV day 1 every 21 days

Primary Endpoint: PFS
Accrual: 625 pts
Open Oct. 2010

**Figure 2. The GOG 262 study.**

**MITO 7**

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<td>Carboplatin AUC 2</td>
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<td>Paclitaxel 60 mg/m² IV</td>
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Primary Endpoint: PFS
Accrual: 800 pts
Open Nov. 2008

**Figure 3. The MITO 7 study.**

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**carboplatin for Japanese patients**

Hematologic toxicity was more frequently observed in the JGOG trial than in previous studies using the same chemotherapy doses in Western countries [22, 23]. There are well-known discrepancies in the observed toxicity of carboplatin-based chemotherapy between Japanese and Western patients [24], which can be explained in part by the different techniques used to assay creatinine. Two techniques are commonly used to measure serum creatinine levels: (i) the kinetic Jaffé method; and (ii) the enzymatic peroxidase–antiperoxidase (PAP) method. The creatinine clearance measured by the PAP method overestimates the GFR in subjects with normal renal function [25], and most clinical laboratories in Japan use the PAP method. Therefore, the carboplatin dose calculated with the Calvert formula using the PAP method would be overdosed in the JGOG trial and induce more myelotoxicity. Several methods to estimate GFR more accurately from serum creatinine have been proposed [26–29]; however, there is no global consensus on the best method for assessing renal function as the basis for determining the dosage of carboplatin. One should be cautious in interpreting carboplatin-induced toxicities and take into account the method used to determine serum creatinine concentrations when using creatinine clearance estimations with the Calvert formula.

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**summary**

In conclusion, dose-dense TC is an effective treatment with improved progression-free survival in patients with advanced ovarian cancer. Confirmatory studies are ongoing in Western countries. GOG 262 (trial registration: NCT01167712; Figure 2) is comparing carboplatin AUC 6 plus 175 mg/m² paclitaxel given every 3 weeks with carboplatin AUC 6 plus weekly 80 mg/m² paclitaxel given every 3 weeks for suboptimal stage III or IV ovarian cancer. Additional bevacizumab is an option in the study. MITO 7 (trial registration: NCT00660842; Figure 3) is comparing carboplatin AUC 5 plus 175 mg/m² paclitaxel with weekly carboplatin AUC 2 plus weekly 60 mg/m² paclitaxel. ICON 8 is preparing to start a three-armed randomized trial comparing carboplatin AUC 5 plus 175 mg/m² paclitaxel with carboplatin AUC 5 plus weekly 80 mg/m² paclitaxel and with weekly carboplatin AUC 1.67 plus weekly 80 mg/m² paclitaxel for stage IC to IV ovarian cancer. It is reasonable to conclude that if these studies confirm the Japanese phase III trial data, then weekly paclitaxel administration is an appropriate strategy to consider in the standard treatment of advanced ovarian cancer.
references