Dose-Dense Chemotherapy in Advanced Ovarian Cancer: Old Idea, New Perspectives

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Background

It is well known that ovarian cancer is the most lethal disease in the gynecological malignancies group (1). At this moment there is no efficient screening method for ovarian cancer and most of the patients with epithelial ovarian cancer are diagnosed in advanced stages.

The current standard of care in advanced ovarian cancer consists of maximum cytoreductive surgical effort followed by chemotherapy - 6 cycles of Paclitaxel 175mg/m² (iv, 3 hours) plus carboplatin AUC 5-7 every 21 days, leading to excellent response rates but also to frequent relapses. Several methods of improving outcomes were intensively studied: addition of a third agent to chemotherapy, addition of anti-angiogenesis drugs – Bevacizumab, intraperitoneal chemotherapy, dose dense chemotherapy. Dose dense chemotherapy regimens rationale is the Norton-Simons model of growth according to which the increasing of dose density of chemotherapy will increase efficacy by minimizing the opportunity for regrowth of tumor cells between cycles of chemotherapy. Several clinical studies using DD regimens were first developed for breast cancer treatment in the neoadjuvant, adjuvant and metastatic disease setting. Taking into account the promising findings of breast cancer clinical trials, the DDC principles were applied in advanced ovarian cancer chemotherapy in the first and second line treatment setting clinical studies. Several regimens including weekly paclitaxel + cisplatin or weekly paclitaxel + carboplatin were investigated with results that proved that dose-dense weekly platinum is an effective therapy in platinum-sensitive as well as in platinum resistant patients. The Japanese Gynecology Oncology Group (JGOG) was the first to demonstrate the survival advantage of dose dense weekly administration of paclitaxel in 2009. Patients were randomly assigned to receive six cycles of either paclitaxel (180mg/m²; 3 hours intravenous infusion) plus carboplatin (area under the curve [AUC] 6 mg/ml per min) given on day 1 of a 21 day cycle – conventional regimen arm with 320 patients) or dose dense (DD) paclitaxel (80mg/m²; 1 hour infusion) given on days 1, 8 and 15 plus carboplatin given on day 1 of a 21-day cycle (dose dense regimen arm with 317 patients). Statistical analysis showed that median progression-free survival was longer in the DDC group (28 months, 95% CI 22.3-35.4) than in the conventional treatment group (17.2 months, 15.7-21.1; hazard ratio [HR] 0.71; 95% CI 0.58-0.88; p=0.0015). Moreover, the 3 years overall survival was higher in the dose-dense regimen group (72.1%) than in the conventional treatment group (65.1%; HR 0.75,0.57-0.98; p=0.03). Hematologic toxicities – neutropenia and severe anemia were higher in the dose dense group but peripheral neuropathy was similar in the two study arms. The ongoing trials for treatment of advanced ovarian cancer include dose-dense chemotherapy arms. Although new biological therapies (bevacizumab) showed its efficacy in ovarian cancer, it is still used in combination with chemotherapeutic agents such as paclitaxel. Such approaches as dose dense administrations are intensively investigated in ongoing trials and the right dosing, frequency is to be established after publication of new emerging data.

Key words: ovarian cancer, dose dense chemotherapy, paclitaxel, carboplatin

This recommendation is supported by level 1 evidence from two large randomized trials, the Gynecologic Oncology group (GOG) study and the Canadian-European Intergroup study that showed the paclitaxel /platinum combination to be superior to the cyclofosfamide/cisplatin combination in terms of survival (3-5) . Despite excellent response rates to standard chemotherapy, in 75% of the complete clinical responses the disease will relapse and most of the patients will die due to progressive disease (4).

Several approaches for improving outcomes of primary treatment for advanced ovarian cancer have been studied. The addition of a third chemotherapeutic agent to the platinum and taxane regimen was the first approach to be investigated but no improvement in survival was realised. Moreover, a third agent brought little else but more severe toxicities (6). The year 2010 was a turning point for ovarian cancer treatment: bevacizumab was proved to improve the survival of patients with ovarian cancer (7, 8). Other justified attempts were intraperitoneal chemotherapy, maintenance chemotherapy and dose-dense chemotherapy.
Basic principles of Dose-Dense Chemotherapy

Dose-dense chemotherapy (DDC) is a chemotherapy administration concept that is being investigated more and more. In order to achieve maximum tumor kill, dose-dense regimens increase the rate of chemotherapy delivery by reducing the interval between each dose, not by increasing the dosage.

Understanding DDC requires the knowledge of tumor cell replication and growth models better known as the Gompertzian growth curve, which is based on Norton Simon’s hypothesis (Fig.1). According to the Gompertzian theory, tumor growth tends to follow a mathematically predictable growth curve, with rapid initial growth succeeded by slower, leveled growth (Fig.2) (9). It is well known that rapidly dividing cells contained by smaller, early stage tumors are more sensitive to chemotherapy. The Norton–Simon model considers that increasing the dose density of chemotherapy will increase efficacy by minimizing the opportunity for the regrowth of tumor cells between cycles of chemotherapy. This is the main principle of DDC with the Gompertzian curve, hitting the tumor cells at the time they are just beginning to grow rapidly again – “hit them while they are down” (10).

Accelerating the chemotherapy administration has its maximal impact in the early (faster growing part of the growth curve). Consequently, delays or interruptions in chemotherapy result in lesser efficacy as the drug acts in the later (flat) part of the gompertzian growth curve. Both intrinsic kinetics of cancer cell growth and the potential effect on tumor blood vessels (inhibition of angiogenesis) contribute to reduce the tumor regrowth.

At the same time, heterogeneity of chemotherapy sensitivity of cancer clones that reflects the evolutionary diversity of any individual cancer is a variable that biases the Norton-Simon mathematical model. This heterogeneity predicts that resistant cancer clones are growing even as sensitive clones are responding to chemotherapy.

Dose-Dense Chemotherapy in Breast Cancer – first positive results

Several clinical studies using DD regimens were first developed for breast cancer treatment in the neoadjuvant, adjuvant and metastatic disease setting. Despite the fact that the theory seems logical, practice showed that the results of DDC regimens in the breast cancer treatment were promising, but not that convincing (11). Clinical studies in women with node-positive breast cancer did not find a statistically significant difference in survival or recurrence rates between DD and classical chemotherapy regimens. However, statistical analysis showed a slightly improved survival and fewer recurrences. Consequently, researchers drew the conclusion that certain subgroups of high risk women with breast cancer (under 50 years old, with ER negative status and/or HER2 positive tumors) would benefit the most from DDC (12). Furthermore, two randomized phase three trials on breast cancer showed improved survival benefit by administering paclitaxel weekly compared with every 21 days administration (12, 13).

Dose-Dense Chemotherapy in Advanced Ovarian Cancer

Even if the prognosis of patients with advanced ovarian cancer has improved significantly by the introduction of paclitaxel/platinum combination chemotherapy and interval debulking surgery, many patients still die of drug resistant disease. Second line chemotherapy has an activity in recurrent ovarian cancer and may result in prolonged secondary remissions and improved quality of life with good symptom control (14). The response to second line chemotherapy is related to platinum sensitivity. Platinum based re-challenge has 60% response rates in the case of platinum sensitive tumors - progression free survival (PFS) >6 month. The response rate falls below 10% in platinum resistant tumors.
resistant patients (with progression during or within 6 months after last platinum chemotherapy) (15).

Several agents such as topotecan, gemcitabine, liposomal doxorubicine, paclitaxel, docetaxel, etoposide were investigated in the second line treatment of ovarian cancer with response rates below 20% in the platinum resistant patients. One distinct group is formed by the intermediate sensitive patients (PFS between 6-12 months) that have response rate ranging from 20 to 35% to the chemotherapy agents mentioned (16). Consequently, intensive efforts were made in order to improve ovarian cancer management including new treatment strategies.

Taking into account the promising findings of breast cancer clinical trials, the DDC principles were applied in advanced ovarian cancer chemotherapy in the first and second line treatment clinical studies.

**Weekly paclitaxel and ciplatin**

In vitro studies with paclitaxel suggested that fractionated brief infusions might be more effective than the standard 3 hours infusion every three weeks. The main rationale of dose dense weekly administration of paclitaxel is the larger percentage of cancer cells to enter the vulnerable phase of their cell cycle when cytotoxic paclitaxel concentrations are present. Moreover, lower doses and the shorter the infusions may lead to reduced myelosupresion and other toxicities compared to the 3 hour infusion (17).

These assumptions were demonstrated in a dose finding phase one study with paclitaxel administrated in one hour, weekly in patients who were previously treated with paclitaxel and cisplatin at conventional intervals. This study demonstrated that the dose limiting toxicity was reached at 100 mg/m$^2$, defining a maximum tolerated dose of 80mg/m$^2$/week. 30% of the patients (4 out of 13 assessable patients) achieved partial responses. The toxicity profile was much improved for the weekly administration: no mucositis or grade 3 neuropathy was seen and the hematologic toxicity was less pronounced compared to the 3-weekly schedule (18). These results, combined with later studies that confirmed the feasibility and activity of the weekly paclitaxel offered the rational to combine weekly paclitaxel with weekly platinum.

FE de Jongh from the University Medical Center Rotterdam performed a phase I/II study in order to investigate the combination of dose dense cisplatin combined with paclitaxel. Weekly cisplatin 70mg/m$^2$ (days 1,8,15 and 29,36,43) was combined with escalating doses of paclitaxel either 4 weekly(135-225 mg/m$^2$) or weekly (60-100 mg/m$^2$), administered over 3h followed by 3 weekly paclitaxel/ platinum. The targeted population consisted of patients with primary epithelial ovarian cancer with first line platinum-based combination induction and patients with progressive disease or relapse after therapy with first line platinum-based combination without previous paclitaxel therapy. 50 patients entered the study and 46 were evaluated: 21 chemo-naive patients and 25 patients with a relapse after platinum-based chemotherapy. Apart from 4 patients that were discontinued due to grade 4 toxicities: neurotoxicity, renal toxicity, cardiac event and one adverse event not related to the therapy, all other patients (24 in the weekly paclitaxel arm and 22 in the 4 weekly paclitaxel arm) received the two dose dense induction cycles. 122 cycles of 4 weekly paclitaxel (arm A) and 134 cycles of weekly paclitaxel/cisplatin (arm B) were administrated. Hematologic toxicity consisted of neutropenia: 24% in arm A versus 19% in arm B; thrombocytopenia in 2.4% versus 4.5%. Other evaluated toxicities were nausea and vomiting in 1% of the cases for arm A compared to 6% in arm B. Response rates were high and similar for both regimes; 95% of the non pretreated patients responded to chemotherapy and 71% achieved complete response. For patients with recurrent disease previously treated with platinum based chemotherapy, the response rate was 85%, with 32% of the cases being complete responses. Median PFS was 24 months for chemotherapy naïve patients and 12 months for recurrent disease. Median survival was 76 and 25 months, respectively. The authors investigated 2 schedules that both doubled the dose intensity of paclitaxel compared to standard 3 weekly paclitaxel/cisplatin cycles. Since the highest dose intensity of paclitaxel in combination with weekly cisplatin was reached with weekly paclitaxel 90mg/m$^2$, this was the scheduled recommended by the authors for further studies (19).

**Weekly paclitaxel and carboplatin**

Taking into account the 3 randomised studies that showed that 3-weekly paclitaxel / carboplatin was as effective and better tolerated as

3 weekly paclitaxel /cisplatin, paclitaxel/carboplatin combination therapy has become the standard regimen in ovarian cancer (20, 21, 22). M.E.L. van der Burg demonstrated that weekly paclitaxel 90mg/m$^2$ can be safely combined with weekly carboplatin area under the curve 4. The study enrolled 62 patients with recurrent epithelial ovarian cancer after at least one platinum-based combination therapy. Median PDI (progression free interval) was 8 months (0-81). 23 patients had a PFI of less than 6 months, 19 patients had a PFI of 6-12 months and 20 patients had a PFI more than 12 months. The median number of prior therapies was 2 (range 1-8). Thirty eight patients had prior treatment with topotecan and 22 patients had at least one prior weekly cisplatin based combination chemotherapy with etoposide paclitaxel or topotecan. The weekly paclitaxel/ carboplatin regimen was well tolerated. Toxicity of 360 administrations included grade 3 or 4 trombocytopenia in 8%, neutropenia in 40% and febrile neutropenia in 1.1%. Treatment was delayed with a median of 1 week (range 1-5 weeks) in 16% of the administrations. No nausea/vomiting or neurotoxicity grad 3 or 4 were observed. Using the weekly paclitaxel/carboplatin regimen led to early responses: 61% of the patients had a response at the completion of the sixth week of the cycle. Taking into account the fact that the study
population was a heavily pretreated one, the overall response rate is 74% and median PFS was 11 months. Consequently, the weekly paclitaxel/carboplatin regimen appears to be very active and is well tolerated. These two studies presented above show that dose-dense weekly platinum is an effective therapy in platinum-sensitive as well as in platinum resistant patients. Both weekly cisplatin/paclitaxel and carboplatin/paclitaxel lead to responses ranging from 46% to 64% in platinum resistant patients.

Various schedules based on dose-dense paclitaxel/carboplatin were investigated. The “Leuven” dose-dense paclitaxel/carboplatin regimen consisting of six courses of paclitaxel (90mg/m²) and carboplatinum (AUC 4) on day 1 and 8 every 3 weeks was investigated in 33 patients with recurrent platinum resistant and platinum sensitive ovarian cancer. Median PFS was 9 months; median OS was 18 months. Median PFS was 6.75 months for the platinum resistant and 10.5 months for the platinum sensitive group. These results published by Isabelle Cadron in the Department of Obstetrics and Gynecology, University Hospital, Leuven confirms that dose dense paclitaxel and carboplatin offers a well tolerated regimen with high response rates even in heavily pre-treated and platinum–resistant ovarian cancer (24).

**Dose dense paclitaxel/carboplatin as front line treatment in advanced ovarian cancer after cytoreductive surgery?**

The Japanese Gynecology Oncology Group (JGOG) was the first to demonstrate the survival advantage of dose dense weekly administration of paclitaxel in 2009 (25). The clinical protocol JGOG3016 enrolled 637 patients with stage II to IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer. Patients were randomly assigned to receive six cycles of either paclitaxel (180mg/m²; 3 hours intravenous infusion) plus carboplatin (area under the curve (AUC) 6 mg/ml per min) given on day 1 of a 21-day cycle (conventional regimen arm with 320 patients) or dose dense (DD) paclitaxel (80mg/m²; 1 hour infusion) given on days 1, 8 and 15 plus carboplatin given on day 1 of a 21-day cycle (dose dense regimen arm with 317 patients). The results published by Dr. Noyuri Katsumata were more than promising. Statistical analysis showed that median progression-free survival was longer in the DDC group (28 months, 95% CI 22.3-35.4) than in the conventional treatment group (17.2 months, 15.7-21.1; hazard ratio (HR) 0.71; 95% CI 0.58-0.88; p=0.0015). Moreover, the 3 year overall survival was higher in the dose-dense regimen group (72.1%) than in the conventional treatment group (65.1%; HR 0.75, 0.57-0.98; p=0.03). Despite the bright side of achieving the primary endpoint of the study – PFS, treatment toxicities were carefully analyzed. 165 patients assigned to the DD regimen and 117 assigned to the conventional regimen discontinued treatment early. Although most reasons for patient dropout were balanced between the groups, withdrawal due to toxicity was much higher in the DD regimen arm than in the conventional arm (113 patients vs. 69 patients). Neutropenia was the most common adverse event: in DD group 92% of the patients developed neutropenic events grade 1-4 respectively 88% in the conventional arm. Severe anemia (grade 3 and 4 CTCAE was more frequent in the DD arm compared to the conventional arm (69% vs 44%; p<0.0001). The frequency of neurotoxicity was similar in both groups. Motor neuropathy affected 5% of the DD regimen group patients compared to 4% in the conventional regimen group. Sensorial neuropathy occurred in 7% of the DD arm versus 6% in the conventional arm (25).

**Strong points of the JGOC study:**

1. It is the first study to show an improved progression free survival in women with newly diagnosed, stage II to IV ovarian cancer for the dose dense treatment with paclitaxel and carboplatin.
2. Toxicities were accurately analyzed. As expected, hematological toxicity (neutropenia and anemia) should be a matter of concern especially in the dose dense group. Fewer than half the patients assigned to the dose dense regimen completed treatment according to the study protocol (26).

**Weak points of the JGOC study:**

1. The study recruited patients only from Japan. Taking into account that the biological features of ovarian cancer might vary according to geographical area, the results cannot be generalized unless a multinational multicentre prospective study confirms the results.
2. The dose-dense chemotherapy regimen used in the trial was also dose-intensive. The study showed a survival advantage with an increased total dose of 240mg/m² given in three divided doses during a 21 day cycle. It cannot be established clearly if the dose density or dose intensity or more probably both of them influenced the positive results.
3. Effects of the two chemotherapy regimens on the quality of life were not assessed.
4. Although the groups were balanced according to routine clinical prognostic factors, reporting of the proportion of patients with not visible (microscopic) residual disease after cytoreductive surgery would have been useful, because these data are a more robust predictor of clinical outcomes than macroscopic residual disease.
5. It is not clear if the overall survival advantage will be maintained since the 5 year survival rates have not been published yet.
6. All the available results date from the pre-bevacizumab era. How the monoclonal antibody influences the outcomes when combined with dose dense regimens could be cleared hopefully by further clinical trials.
Future perspectives opened by the JGOC-3061 trial

The findings of the JCOG trial are important but they did not change practice at once. It is clear that the results of the Japanese trial have clearly influenced the design of actual clinical trials.

Three major randomized trials in advanced ovarian cancer are ongoing. The GOG262 trial, closed in early 2012, compares the same treatment arms as the Japanese trial – conventional versus three weekly paclitaxel and carboplatin in stage III and IV patients (27). The Multicenter Italian Trials in Ovarian Cancer Group developed the MITO7 study that compares the efficacy and toxicity of weekly administration of carboplatin (AUC2) plus weekly administration of paclitaxel (60mg/m²) (28). Finally, ICON8 –ENGOT OV-13 trial compares standard treatment (every 21 days administration on paclitaxel + carboplatin) with dose dense weekly administration of paclitaxel and every 3 weeks administration of carboplatin and dose dense weekly administration of both paclitaxel and carboplatin (29).

These three studies are meant as confirmatory studies for the JGOC trial but they will also try to answer two major questions: “Does dose dense carboplatin also contribute to improve survival?” and “Will the simple division of total dose of paclitaxel show similar efficacy with less toxicity?”. The results are eagerly awaited.

Conclusions

The main rationale for weekly paclitaxel administration in combination with platinum is the possibility of increasing dose density. This dose dense schedule results in extensive cumulative exposure that has the potential to increase the drug efficacy against slow-growing tumours and reduces the emergence of drug resistant clones. Furthermore, the weekly moderate dosing of paclitaxel also reduces side-effects compared with the 3 weekly high dosing schedule and seems to be effective even in patients who no longer respond to 3 weekly paclitaxel administration.

The ongoing trials for treatment of advanced ovarian cancer include dose-dense chemotherapy arms. Although new biological therapies (bevacizumab) has shown its efficacy in ovarian cancer, it is still used in combination with chemotherapeutic agents such as paclitaxel. Such approaches as dose dense administrations are being intensively investigated in ongoing trials and the right dosing, frequency will be established after the publication of new emerging data.

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