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The Current Situation of Dose-Dense Chemotherapy for Ovarian Carcinoma

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Abstract

Ovarian cancer is the leading cause of death from gynecological malignancies. Despite all the years of research, high relapse rates after the standard front-line treatment for advanced disease could not be reduced. Alternative schedules, dosage and agents are under investigation to achive better efficacy and tolerability. The concept of 'dose-dense therapy' in which the cumulative drug dose remains constant, but the same amount of drug is administered over a shorter period is promising with an acceptable toxicity profile. The Japanese trial of JGOG with advanced epithelial ovarian cancer showed promise in terms of improvement in survival rates by dose dense weekly paclitaxel and carboplatin. The results of the study had encouraged investigation on dose-dense therapy. Although the preliminary data of the latter studies has not been that much confirmatory forthcoming data will illuminate to validate avaible data. In this review, we aim to provide an update on the avaible data and review the role of dose-dense therapy in the treatment of ovarian cancer.

Keywords

Carboplatin, Dose-Dense Chemotherapy, Ovarian Cancer, Paclitaxel

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1. Introduction

Despite all the years of research, the number of deaths due to ovarian cancer could not be reduced. Unfortunately, 50-70% of patients with epithelial ovarian cancer (EOC) achieve complete clinical remission with first-line chemotherapy (CT); however most of them will have recurrence of the disease within 12 to 18 months (1). The standard treatment for advanced ovarian cancer has been platinum-based chemotherapy subsequent to surgery as a first-line treatment. Conventional first-line chemotherapy for ovarian cancer consists of intravenous (IV) paclitaxel (175 mg/m^2) administered over 3 hours, followed by IV carboplatin at an AUC of 5–6 mg/mL per minute, which is repeated every 3 weeks for 6 cycles. The high recurrence rates after initial therapy have prompted researchers to search for alternative schedules, dosage and agents. The rationale for dose-dense CT is in relation with dose-intensity which means unit dose of CT administered per unit time. In this approach, cumulative drug dose remains constant, but the same amount of drug is administered over a shorter period. Dose-dense CT was first demonstrated in breast cancer and has been attended in after the in-vitro demonstration of logarithmic decrease of cancer cell survival fraction when drug concentration was increased in preclinical trials (2, 3). After breast cancer, studies headed to other cancer types to improve the survival rates like lymphoma and ovarian carcinoma. The studies are ongoing with various drug regimens and combinations in dose-dense format. This review article aims to summarize the results of several recent clinical trials addressing dose-dense CT within adjuvant ovarian cancer treatment and discuss their implications for clinical practice.

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2. Overview Analysis

GOG performed a large study to assess the effect of dose-dense CT in patients with advanced stage cancer. 458 patients were included in the study and randomized into 2 groups; low-dose cisplatin (50 mg/m^2) + cyclophosphamide 500 mg/m^2 in every 3 weeks for 8 cycles group and high-dose cisplatin (100 mg/m^2) + cyclophosphamide 1000 mg/m^2 in every 3 weeks for 4 cycles group (4). Both regimens were consisted of the same total dose but, intense dose was given in half-time. No significant difference was observed between 2 groups for progression-free survival (PFS) and overall survival (OS). Hematologic, gastrointestinal, febrile episodes, septic events, and renal toxicities were significantly more common and severe in the dose-intensive group. Thus, results of this study showed that dose intensity wouldn't increase therapeutic efficacy of cisplatin and cyclophosphamide. Correlatively, other randomized trials for cisplatin dose intensity didn't indicate clinical advantage (5). Fuscio et al. randomized, open label, phase 3 clinical trial (1988-1992) compared the efficacy and safety of a dose-dense regimen of single-agent cisplatin with a standard 3-weekly schedule in first-line CT for advanced EOC. Two hundred eighty-five patients were randomly assigned to the experimental dose-dense arm (cisplatin 50 mg/m^2 weekly × 9 cycles) or to the control (standard treatment) arm (cisplatin 75 mg/m^2, administered on day 1 every 21 days × 6 cycles). After a median follow-up of 16.8 years, no differences were observed between the two treatments in PFS (experimental arm: 17.2 months; control arm: 18.1 months) and in OS (experimental arm: 35 months; control arm: 32 months). The study concluded with no significant improvement in PFS or OS by increasing dose intensity of cisplatin compared with standardCT. The major limitation of the study was that current standard therapy for EOC is the carboplatin/paclitaxel combination, whereas they used cisplatin alone, which was the standard therapy when they started the trial. So the results cannot be generalized (5).

In studies that were maintained by National Cancer Institute (NCI), hypertonic saline with high dose cisplatin was used to increase response rates and reduce nefrotoxicity. Complete response rates of patients with large residual volume with NCI regimen didn't differ from the GOG studies with CAP (cyclophosphamide + adriamycin + cisplatin) (11% vs. 12%). Complete response rates of patients with small residual volume also didn't revealed significant difference from GOG's combination of 2 drugs (cisplatin + cyclophosphamide), (38% vs. 32%) (6).

On the other hand, 631 patients with stages II to IV EOC were randomized into two groups in JGOG 3016 trial that was maintained by Japanese Gynecologic Oncology Group; carboplatin + paclitaxel in every 3 weeks group and carboplatin (an AUC of 6 mg/mL per minute, on day 1) in every 3 weeks + weekly paclitaxel regimen (80 mg/m^2, days 1, 8, and 15) group. Treatment was completed to 9 cycles in both groups. After follow-up for median 77 months, an increase in PFS (median: 28 vs. 17 months) and OS (median: 100 vs. 62 months) was observed in dose-dense treatment group in comparison with conventional treatment group. The patients who underwent suboptimal cytoreduction benefited most from dose-dense treatment. An increase in PFS (median: 17 vs. 12 months) and OS (median: 51 vs. 33 months) was observed in this group of patients when compared with conventional treatment. However, statistically significant difference wasn't observed in patients who had undergone optimal cytoreduction. Subgroup analysis of this study revealed that dose-dense treatment improved PFS and OS in histological types except mucinous and clear cell when compared with conventional method (7). Despite its favorable outcomes in survival rates; dose-dense treatment resulted with reduced treatment continuity due to toxicity (52% vs. 37%) and suspense of at least one cycle (76% vs. 67%) (7, 8). Hematologic toxicity was the most common reason for treatment discontinuation and was significantly more frequent among patients assigned to dose-dense treatments (60% versus 43%). However, no difference was detected between dose-dense group and 3-weekly group regarding neurotoxicity (3% versus 7%). Based on these results, dose-dense paclitaxel and carboplatin was suggested as potential new standard for first-line CT in patients with advanced EOC. But it should be noted that authors of this study also remarked that most of the patients were white and Asians had responded better to high-dose treatment (7,8). According to the following quality-of-life results from this trial; the compliance rates with regard to quality of life assessment were 74.5% and 73.0%, respectively, after three CT cycles; 86.8% and 86.9%, respectively, after six CT cycles; and 74.2% and 71.6%, respectively, at 12 months after randomization. The overall quality of life did not differ significantly between the two treatment groups up to 12 months after randomization ($P = 0.46$) (9). These findings justify further investigation into the prevention and treatment of neurotoxicity in order to improve quality of life.

The major toxicity of dose-intensive regimens is myelosuppression and this dose-limiting toxicity does not allow for consistent full dosing. In addition, decreasing the time between dose administration and increasing the dose of an agent may conclude with relative drug resistance. In the last decade, peripheral blood progenitor cells and autologous bone marrow transplantation to support multiple courses of high-dose CT administered at frequent intervals has been employed also. The use of autologous bone marrow and/or peripheral blood progenitor cells (stem cells) allows for

increases in dose intensity of threefold or more for several agents, including alkylators, carboplatin, and mitoxantrone. However most of the reports with high dose CT autologous bone marrow transplantation have been phase 2 trials of patients with a mixed response to first-line CT (10).

European Group for Blood and Marrow Transplantation (EMBT) reported the results of 91 patients in first complete remission treated with high-dose CT and autologous bone marrow transplantation. At a median follow-up of 48 months, median PFS and OS were 21.2 and 44.4 months, respectively. They were unable to recognise prognostic parameters and identify subgroups that significantly benefit from this regimen. However, the small group of patients with no residual disease after surgery show a sustained PFS and OS benefit. These reported median survivals are not significantly better than that with use of paclitaxel as second-line therapy (11).

3. As second-Line Therapy of Ovarian Carcinoma

Alternative manipulations of the dosing schedule of platinum and taxane has been suggested as a method of greater activity and less toxicity in both platinum-sensitive and platinum resistant disease also (12,13). The studies aimed to investigate whether a weekly regimen indeed is more effective than 3-weekly paclitaxel/carboplatin in the management of platinum-resistant/sensitive recurrent EOC previously treated with 3-weekly paclitaxel/carboplatin. Cadron et al included 33 patients with a median number of prior treatment regimens of 2. They reported response rates of 38%, 73% and 80% after the weekly paclitaxel/carboplatin therapy for the platinum resistant, intermediate platinum-sensitive and platinum-sensitive patients, respectively. Toxicity is an important consideration for patients with recurrent disease for whom especially CT is palliative. In this study toxicity was mostly bone marrow-related with neutropenia grade 3/4 in 34% and neutropenic fever in 2% of courses (14). Sharma et al. reported their experience of extended weekly carboplatin and paclitaxel in twenty patients with platinum-resistant/refractory ovarian cancer. The study population received carboplatin AUC 3 and paclitaxel 70 mg/ m^2 on day 1, 8, 15 q 4 weekly for 6 planned cycles. Median PFS was 7.9 months and OS was 13.3 months in the study. One patient experienced grade 4 neutropenia. No grade 3/4 thombocytopenia was reported (15). van der Burg et al. reported promising response rates of 51%, 60% and 61% after the weekly paclitaxel/carboplatin therapy for the platinum-resistant, intermediate platinum-sensitive and platinum-sensitive patients, respectively (16,17). Thirty two patients with recurrent EOC who had received 3-weekly carboplatin and paclitaxel before were enrolled in another study reported by Sharky et al. Weekly taxel at a dose of 80 mg/m^2, followed by weekly carboplatin AUC 2 on day 1, 8, and 15 of a 28-day cycle for 6 planned cycles were administered. For the platinum-resistant, intermediate platinum-sensitive and platinum-sensitive patients the overall response rate was 44.4%, 60% and 76.9%, respectively. PFS was 6.13, 9.1 and 12.17 months, for the 3 groups, respectively. OS was 9.17, 15.2, and 19.23 months, for the 3 groups, respectively. In the study, treatment-related adverse events were manageable with only 1 patient (3.1%) suffering from grade 4 neutropenia. Grade 3 hematological and non-hematological toxicities were neutropenia in 25%, and peripheral neuropathy in 12.5% patients, respectively. The frequency of these toxicities was somewhat nearly similar to the other studies (18).

Although the studies concluded with well tolerated high response rates, final conclusions about the superiority of the regimen for platinum resistant and sensitive disease needed prospective randomized studies with larger numbers of patients to be analyzed.

4. Forthcoming Data

Multicenter Italian Trial in Ovarian Cancer (MITO-7) assessed whether a weekly schedule of carboplatin plus paclitaxel is more effective than the same drugs given every 3 weeks. In this study, 810 patients of stage 1C to 4 EOC were randomized into two groups; conventional three-weekly regimen of carboplatin (AUC 6) plus paclitaxel (175 mg/m2) for 6 cycles or weekly regimen of carboplatin (AUC 2) plus paclitaxel (60 mg/m2) for 18 weeks. MITO-7 was presented at the 2013 American Society of Clinical Oncology (ASCO) Annual meeting and recently published in Lancet Oncology (10,11). As it was presented; the results of weekly treatment and standard regimen were similar for PFS (median PFS was 17.3 months (95% CI 15.2-20.2) in patients assigned to treatment every 3 weeks, versus 18.3 months (16.8-20.9) in women allocated to the weekly schedule) (19). Besides, serious toxicity associated with treatment was less frequent in weekly treatment group and Pignata et al. reported that this regimen had a favorable toxicity profile in elderly ovarian cancer patients, when treated in first line. Fewer patients assigned to the weekly group than those allocated treatment every 3 weeks had grade 3-4 neutropenia (42% vs 50%), febrile neutropenia (0-5% vs 3%), grade 3-4 thrombocytopenia (1% vs 7%), and grade 2 or worse neuropathy (6% vs 17%). Three deaths during the study were attributed toCT; two women died who were allocated treatment every 3 weeks and one death was recorded in the group assigned the weekly regimen (20).

The results were significantly different from the Japanese data but it should be noted that scheduling used in the MITO-7 was quite different from that used in the JGOG 3016. Paclitaxel was given at a lower dose (60 mg/m^2 versus 80 mg/m^2) and carboplatin was administered at an AUC of 2 mg/mL per minute every week in MITO-7. In addition, the different populations of the study groups, the Asian and European, might effect these different clinical outcomes. Although it is promising in some ways, long-term follow-up outcomes of this procedure haven't been published, yet.

Table 1. Protocols of some trials for dose-dense paclitaxel and carboplatin administration.

Trial	Study design	Study arms
JGOG3016 (n=484)	Stage II-IV ovarian cancer	* Carboplatin AUC 6 q3 weeks + Paclitaxel 175 mg/m^2 q3 weeks x 6 cycles * Carboplatin AUC 6 q1 weeks + Paclitaxel 80 mg/m^2 q1 week x 6 cycles
MITO-7 (n=810)	Stage IC-IV ovarian cancer	* Carboplatin AUC 5-6 q3 weeks + Paclitaxel 175 mg/m^2 q3 weeks x 6 cycles * Carboplatin AUC 2 q1 week + Paclitaxel 60 mg/m^2 q1 week x 6 cycles
GOG-262 (n=692)	Newly diagnosed stage II, III or IV disease following surgery; stage III (macroscopic residual disease) or stage IV disease.	* Carboplatin AUC 6 q3 weeks + Paclitaxel 175 mg/m^2 q3 weeks x 6 cycles * Carboplatin AUC 6 q3 weeks + Paclitaxel 80 mg/m^2 q1 week x 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
ICON-8	Stage IC-IV disease, after immediate primary surgery or receive neoadjuvant chemotherapy +delayed primary surgery after cycle 3.	* Carboplatin AUC 6 q3 weeks + Paclitaxel 175 mg/m^2 q3 weeks x 6 cycles * Carboplatin AUC 5 q3 weeks + Paclitaxel 80 mg/m^2 q1 week x 6 cycles * Carboplatin AUC 2 q1 weeks + Paclitaxel 80 mg/m^2 q1 week x 6 cycles

In GOG 262 trial, stage 2 to 4 EOC patients who underwent optimal or suboptimal cytoreduction were randomized into two groups; standard carboplatin + paclitaxel or dose-dense CT (carboplatin in every 3 weeks + weekly paclitaxel) groups(21). Bevacizumab (15 mg/kg every 3 weeks) beginning with cycle 2 (this was administered every 3 weeks for 6 cycles, followed by maintenance bevacizumab until the occurrence of progression or adverse effects) was administrated optionally in both groups to about 80% of patients. A further consideration is that low-dose paclitaxel may also exhibit antiangiogenic activity (22). Most of the patients were in stage 3 or 4 and gross residual disease was present in the time of admission. No significant difference was detected between dose-dense treatment and conventional treatment for PFS in this study which was presented at 2013 European Society for Gynecological Oncology Annual Meeting (HR 0.97, 95% CI 0.79-1.18) (21). However, the results varied due to bevacizumab administration. Dose-dense treatment improved PFS rates when compared with conventional treatment (median: 14 vs. 10 months) in patients who were not treated with bevacizumab (n=112). PFS was similar in dose-dense and conventional treatment groups (median: 15 months for both groups) in patients who were treated with bevacizumab (n=580).

To define the role of dose-dense CT and effects of bevacizumab in total survival, completion of GOG 262 trial is being expected (21, 23). The ICON8 trial is the largest trial of dose-dense therapy in ovarian cancer which is an ongoing tri-armed phase 3 trial. The purpose of this study is to determine if weekly CT is more effective than standard CT (paclitaxel and carboplatin given once every three weeks over 18 weeks) in treating ovarian cancer (24). To this end, it is comparing the 3 possible schedules of treatment (3-weekly carboplatin and paclitaxel, weekly carboplatin plus weekly paclitaxel, and weekly carboplatin and paclitaxel). A point to be emphasized is that ICON8 is the first trial designed to permit variation in timing of surgery; randomization is stratified by immediate primary surgery/delayed primary surgery. The investigators also search for more or fewer side-effects than standardCT. These forthcoming data are awaited with considerable interest to validate the dose-dense therapy.

5. Conclusion

Some clinics prefer dose-dense CT regimen (carboplatin in every 3 weeks + weekly paclitaxel for 15 weeks) rather than conventional procedure for patients who had undergone suboptimal cytoreduction when the histological type was not mucinous or clear cell. This administration was indicated as one of the standard treatments in the algorithms that 2014 National Comprehensive Cancer Network (NCCN) has published (Firstly took part in 2010 algorithm) (25). However, there is no consensus in this issue yet. Dose-dense therapy had been introduced and evaluated in large randomized trials in ovarian cancer (Table.1) however still includes concerns for both efficacy and toxicity profiles. It is reasonable to conclude that if the forthcoming data confirm the Japanese phase 3 trial data, then weekly paclitaxel administration will replace as the standard treatment strategy of advanced ovarian cancer. Determining who will benefit is the focus of current studies in ovarian cancer. Further studies and long-time follow-up results are needed to define the optimal

regimen, combination and the patient population that will receive the greatest benefit from dose-dense strategy.

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