



Controversies on the treatment of ovarian cancer with dose-dense chemotherapy

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Abstract: Epithelial ovarian cancer is the most lethal gynaecological malignancy with an estimated 295,414 new cases and 184,799 deaths around the world. Cytoreductive surgery and combination chemotherapy have remained a standard therapy for decades. The majority of women diagnosed with ovarian cancer will receive systemic chemotherapy for recurrent or advanced diseased. In recent years, therapies such as anti-angiogenics, PARP inhibitors, and dose-dense chemotherapy have emerged as novel strategies against ovarian cancer. Dose-dense chemotherapy, usually with a carboplatin and paclitaxel regimen, has been proposed as an alternative to conventional chemotherapy for these patients. However, the results for different trails are inconsistent and dose-dense chemotherapy remains controversial. Results from the JGOG 3016 study showed a progression free survival and overall survival benefit, with increased neurotoxicity and anaemia. While the GOG 262, MITO-7, GOG 252 and ICON8 studies found no benefit on progression free survival, with a recent meta-analysis concluding that three weekly chemotherapy remains the standard of care. Ovarian cancer molecular subtypes and differences in pharmacogenetics between populations may explain the differences in response to dose dense chemotherapy, however our understanding of this factors is still lacking. Here, we reviewed the evidence for and against dose-dense chemotherapy and the possible factors for the different results among trials.

Keywords: Epithelial ovarian cancer (EOC); chemotherapy; taxanes

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Introduction

Epithelial ovarian cancer (EOC) is recognized as a heterogeneous disease with the highest lethality among gynaecological malignancies. In 2018, the GLOBOCAN database estimated there were 295,414 new cases and 184,799 deaths from EOC (1). The GLOBOCAN database predicts that by 2040 there will be a worldwide increase in incidence and mortality, reaching 434,184

new cases and 293,039 deaths per year respectively (2). The majority of women are diagnosed with advanced International Federation of Gynaecology and Obstetrics (FIGO) stage III/IV disease and over 75% of patients diagnosed with ovarian cancer will recur and die from this disease. Cytoreductive surgery and combination platinum-taxane chemotherapy have remained a standard therapy for decades. Other systemic therapies such as anti-angiogenics,

PARP inhibitors, and dose-dense chemotherapy have emerged as novel strategies against ovarian cancer (3,4).

In principle, the cancer cell has a higher exposure with a dose-dense approach, therefore limiting the surge of resistance in those cells; this in turn enhances the antineoplastic activity. Additionally, when using paclitaxel once a week, instead of three-weekly, an anti-angiogenic effect is in place (5). In a phase II study, 80 mg/m² paclitaxel and carboplatin at a target area under the curve (AUC) of 2, were administered every week to recurrent ovarian cancer patients, a 67% response rate was achieved (6), which led to phase III studies that were revised in various publications and guides (7–10). However, dose-dense chemotherapy and its benefits remain controversial, so we revised the main studies to help guide the decision on the use of this type of chemotherapy.

Dose-dense therapy: evidence found in phase III studies

The Japanese Gynecologic Oncology Group's (JGOG) 3016 New Ovarian Elaborate (NOVEL) (11) study was the first phase III clinical trial to include 637 patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer in stages two to four; individuals were assigned randomly to regimes of dose-dense paclitaxel and carboplatin or conventional treatment. After a median follow up of 76.8 months, the median progression free survival (PFS) was better in those individuals with a dose-dense regime (28 months) than those in the three weekly (17.2 months), with a statistically significant hazard ratio (HR) of 0.71 [95% confidence interval (CI): 0.58–0.88]. Furthermore, the overall survival (OS) favoured the paclitaxel dose-dense group with an HR of 0.75 (95% CI: 0.57 to 0.98, *P*=0.03). On the other hand, there was no significant difference in the response rate between arms.

The most common adverse event was neutropenia with 286 of 312 patients (92%) in the dose-dense regimen and 276 of 314 patients (88%) in the conventional regimen. A statistically significant difference of anaemia (grade 3/4) was found, with a higher prevalence in the subjects with the dose-dense treatment (69%) compared to the other group (44%). The frequencies of other toxic effects were similar between groups (11). Median overall survival was 100.5 months in the dose-dense treatment group and 62.2 months in the conventional treatment group (HR 0.79, 95% CI: 0.63–0.99; *P*=0.039). With these results, dose-dense chemotherapy was seen as a possible new standard for

treatment in 2013 (12).

The Multicentre Italian Trials in Ovarian cancer trial (MITO-7) (13), initiated an open label trial with 810 individuals with ovarian cancer in a FIGO stage IC to IV, 404 patients received standard chemotherapy with carboplatin (AUC 6 mg/mL/min) and paclitaxel (175 mg/m²) three weekly for a total of six cycles and 406 patients received an established regimen of weekly carboplatin (AUC 2 mg/mL/min) plus paclitaxel (60 mg/m²) for 18 consecutive weeks. The weekly regimen did not have a beneficial effect over PFS, having an HR of 0.96 (95% CI: 0.8 to 1.16, *P*=0.66). However, it was associated with a better quality of life and a lower toxicity rate, making such regimen an alternative for poor performance status patients. Noted, strictly a dose-dense paclitaxel method was not used.

The most common adverse events found in the every 3 week treatment group, were grade 3–4 neutropenia in 167 of 399 patients (42%) compared to 200 out of 400 patients (50%) in the weekly group, febrile neutropenia (2 *vs.* 11), thrombocytopenia grade 3–4 (4 *vs.* 27), and neuropathy grade ≥2 (24 *vs.* 68) (13).

An open-label and randomized phase 3 trial—the GOG 0262 study (14), included 692 patients with ovarian cancer. Two regimens were compared, the first one included intravenous paclitaxel at a 175 mg/m² dose, administered as a 3 hours infusion on the first day in addition to intravenous carboplatin at an AUC of 6, also on day 1 of the cycle, and a total of six cycles (21-day cycle). The second regimen included 80 mg/m² of body surface area intravenous paclitaxel, over one hour on days one, eight, and fifteen (21-day cycle), in addition to intravenous carboplatin (AUC =6) on the first day of each of the total 6 cycles. At the median 28 months follow-up, there was a 67% survival rate. The intention-to-treat analysis revealed a lack of effect in PFS of the weekly paclitaxel compared to the one administered every three weeks [14.7 compared to 14 months; HR 0.89 (95% CI: 0.74–1.06, *P*=0.18)]. An ancillary analysis in individuals who did not receive bevacizumab, PFS was improved significantly by the weekly paclitaxel regimen, adding 3.9 months of PFS when compared to the other regimen. This points to the possible additive effect of anti-angiogenic therapy in adjuvant treatment. On the other hand, those in the weekly paclitaxel group experienced more frequently grade 3–4 anemia and also of grade 2–4 neuropathy; with a lower frequency of grade 3–4 neutropenia.

In the recent ICON 8 trial (15), where 1,566 women with an epithelial ovarian cancer in a FIGO stage IC to IV

were included after primary cytoreductive surgery (IPS) or before receiving neoadjuvant chemotherapy for intended delayed primary cytoreductive surgery (DPS). Study population characteristics were a median age of 62 years, 93% had a good performance status (ECOG 0 or 1), 69% had high grade serous carcinoma, and 72% presented with advanced (stage IIIC) disease. There were three groups randomly assigned, each receiving a different regimen (1:1:1): group 1 carboplatin at either AUC5 or AUC6 and paclitaxel 175 mg/m² every first day of a three-week cycle for a total of 6 cycles; the second group received the same 6 cycles of three weekly carboplatin dose in addition to weekly paclitaxel 80 mg/m²; and the third group was given weekly carboplatin AUC2 and paclitaxel 80 mg/m² for a total of 18 weeks. None of the weekly regimens showed a PFS improvement and OS is not reported. A higher incidence of uncomplicated neutropenia in the dose-dense groups, with 15% vs. 35% vs. 30% in groups 1, 2 and 3 respectively. Febrile neutropenia occurred in 4%, 6% and 3% of patients respectively. No difference in sensory neuropathy of grade ≥ 2 was observed between groups.

In a meta-analysis published by Marchetti *et al.* (16), four randomized controlled trials were included with a total of 3,698 patients. In such study, it was determined that dose-dense chemotherapy does not significantly improve PFS (HR 0.92, 95% CI: 0.81–1.04, P=0.20) versus standard regimen. With the absence of PFS superiority of dose-dense schedule, the authors conclude that the standard of care for advanced EOC should continue to be the conventional every 3-week schedule.

Factors associated to dose-dense chemotherapy response

Dose-dense chemotherapy in ovarian cancer remains a controversial topic, as seen in the studies previously described. Different factors influence the results to dose-dense therapy. Histological and molecular subtypes with diverse clinical features, chemotherapeutic responses and prognoses, as identified by Tan & cols. (17), 5 molecular subtypes (Epithelial-A, Epithelial-B, Mesenchymal, Stem-like-A, and Stem-like-B) of EOC, being Stem-like-A the one with the worst prognosis along with increased microtubule activity that would render this group more resistance to paclitaxel. The Australian Ovarian Cancer Study (AOCS) and The Cancer Genome Atlas (TCGA) also identified subtypes based on genomic profiling of high-grade serous ovarian carcinoma: mesenchymal, immunoreactive, differentiated

and proliferative. Of these subtypes, the mesenchymal has the poorest OS (median of 26.3 months) (18). The difference in survival among the four molecular subtypes may be due to difference in their response to chemotherapy, some having a higher resistance to platinum therapy, but higher sensitivity to taxanes, as seen in the Japanese Gynecologic Oncology Group study (JGOG3016A1), where conventional and dose-dense carboplatin plus paclitaxel were compared among the four subtypes. Altogether, the mesenchymal subtype exhibited the worst PFS (median 1.4 y) and OS (median 3.6 y). With the previously stated, the mesenchymal subtype had a better outcome in the dose-dense group than in the conventional chemotherapy group, resulting in a longer PFS (median 1.8 y versus 1.2 respectively) (18).

Another important factor to consider when using dose-dense chemotherapy is the relationship that Breast Cancer (BRCA) 1/2 mutations have with a decreased sensitivity to taxanes. Furthermore, BRCA 1 may prove useful as a predictive biomarker to platinum chemotherapy in EOC, with BRCA1 deficiency anticipating greater response, although it also reduces response to taxanes (19).

Finally, it is important to stress that genetic differences, in addition to the pharmacogenetics of taxanes, have been proposed as the reason behind the variability in outcomes to dose-dense chemotherapy between the Japanese and Western populations. Genetic variations that come with ethnic differences may influence the pharmacokinetics and pharmacodynamics of paclitaxel (20). The cytochrome CYP3A5 gene allele found in Caucasian patients is non-functional, contributing to an increase in toxicity due to a lower metabolism of paclitaxel (21). A normal CYP3A5 function is more frequently seen among African-American population (73%) followed by Japanese (29%) and Caucasians (22). However, there is still a gap to be filled regarding the role and clinical implications of these pharmacogenetic variability.

Conclusions

The benefit of dose-dense regimen remains controversial, the only positive study is JGOG 3016, where a benefit in PFS and OS was observed, displaying only increases in neurotoxicity and anaemia. However, there are 4 negative studies where there is no impact on PFS (GOG 262, MITO-7, GOG 252 and ICON8) and one study with no OS benefit (MITO-7), with a meta-analysis concluding that three weekly chemotherapy remains the standard of care. Dose-dense chemotherapy can be used safely in the

treatment for EOC but does not significantly improve survival outcomes compared with standard three weekly chemotherapy in western populations. In order to have a true individualized systemic therapy, factors from different perspectives such as clinical, genetic and histological studies should be incorporated in future trials.

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