

## Review Article



# Weekly versus 3-weekly paclitaxel in combination with carboplatin in advanced ovarian cancer: which is the optimal adjuvant chemotherapy regimen?

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## ABSTRACT

The 3-weekly regimen of carboplatin and paclitaxel is the backbone of first line adjuvant chemotherapy for advanced ovarian cancer. The landmark Japanese Gynaecologic Oncology Group (JGOG) 3016 study demonstrated significant improvements in progression-free survival and overall survival with dose dense weekly administration of paclitaxel in combination with 3-weekly carboplatin. However, efforts to replicate these benefits have failed in subsequent phase III trials. Weekly paclitaxel is purported to have enhanced antitumor activity, with stronger anti-angiogenic effects, and yet is better tolerated. In this review, we explore the rationale for dose dense weekly paclitaxel, and compare the relevant trials as well as quality of life considerations. Possible reasons for the difference in outcomes between the JGOG 3016 and other studies are reviewed, with a focus on how the addition of bevacizumab, the variations between histological and molecular subtypes of epithelial ovarian cancers, and ethnic pharmacogenetic differences may potentially affect the efficacy of dose dense paclitaxel.

**Keywords:** Epithelial Ovarian Cancer; Paclitaxel; Chemotherapy; Pharmacogenetics

## BACKGROUND

Over the last decade, optimal treatment for women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer has been cytoreductive surgery and platinum-based combination chemotherapy [1]. The chemotherapy backbone of 3-weekly carboplatin and paclitaxel for the first line adjuvant treatment of ovarian cancer was established following the studies by McGuire et al. [2] showing superior progression-free survival (PFS) and overall survival (OS) for cisplatin with paclitaxel over cisplatin and cyclophosphamide; the subsequent Gynecologic Oncology Group (GOG) 158 study which showed non-inferiority of carboplatin and paclitaxel compared with cisplatin and paclitaxel [3]; and the GOG 0182-ICON5 study which failed to demonstrate superiority of adding a third cytotoxic agent (gemcitabine, methoxypolyethylene glycosylated liposomal doxorubicin, or topotecan) to standard carboplatin and paclitaxel [4].

In 2013, the Japanese Gynaecologic Oncology Group published a landmark study (JGOG 3016) demonstrating significant improvements in PFS and OS with the dose dense administration of paclitaxel (80 mg/m<sup>2</sup> weekly) combined with 3-weekly carboplatin over the established standard 3-weekly administration of both drugs [5]. However, subsequent phase III studies in western populations have failed to demonstrate PFS and OS benefit of dose dense weekly paclitaxel [6]. In this review, we will explore the rationale for dose dense weekly paclitaxel and the possible reasons behind the difference in outcomes between JGOG 3016 and other phase III trials evaluating dose dense weekly paclitaxel in the first line treatment of ovarian cancer.

## RATIONALE FOR DOSE DENSE WEEKLY PACLITAXEL

The key scientific rationale for weekly paclitaxel administration is to facilitate increased dose density of paclitaxel administration. Theoretically, in tumor growth kinetics, the exponential phase of the Gompertzian tumor-growth curve has the highest proportion of tumor cells undergoing mitosis [7]. It is here when tumor cells are most sensitive to the cytotoxic effects of paclitaxel, which inhibits mitosis in the late G2-M phase of the cell cycle. The dose dense approach allows constant exposure of paclitaxel to this phase, and potentially limits the emergence of resistant cell populations, thus enhancing antitumor activity from greater drug exposure [8].

It has also been suggested that weekly paclitaxel may have a direct anti-angiogenic effect when compared with the 3-weekly regimen [9]. The anti-angiogenic properties of paclitaxel have been demonstrated at cytostatic concentrations (less than 10 nM). Increased dynamic instability of interphase microtubules in endothelial cells, a slower metaphase to anaphase transition, and inhibited endothelial cell migration are some mechanisms of cytostasis observed at low in vitro concentrations of paclitaxel. Acquired resistance to the cytotoxic effects of 3-weekly paclitaxel could possibly be reversed by the weekly administration, which has better anti-angiogenic and vascular disruption effects [8].

Finally, the weekly paclitaxel regimen would theoretically also be better tolerated than the 3-weekly schedule. The severity of myelosuppression is dependent on the duration at which plasma concentration of paclitaxel is above 50 nM [9,10]. Hence, the shortened infusion time of 1 hour and weekly dose of 60–80 mg/m<sup>2</sup> could potentially reduce myelosuppression, while maintaining greater dose intensity compared to the 3-weekly dose of 175 mg/m<sup>2</sup>. Plasma concentrations of paclitaxel 80 mg/m<sup>2</sup> given weekly over 1 hour have a quicker rate of decline than 175 mg/m<sup>2</sup> administered over 3 hours every 3 weeks, thus minimizing dose-limiting toxicities [9].

In several prospective phase II trials, weekly paclitaxel alone was deemed to be a potentially effective agent in both platinum-sensitive and platinum-resistant recurrent epithelial ovarian cancer, with response rates ranging between 20% and 62% [11-13]. Some of these studies also demonstrated efficacy in paclitaxel resistant ovarian cancer, with a response rate of 25% being reported in patients whose cancers had progressed during treatment, or recurred within 3 months of 3-weekly paclitaxel [14].

## PHASE III STUDIES OF DOSE DENSE VERSUS 3-WEEKLY PACLITAXEL

The promising results of these earlier phase II trials led to a series of phase III trials comparing weekly paclitaxel with 3 weekly paclitaxel in the adjuvant setting, which are summarized in **Table 1**.

The JGOG 3016 study was the first phase III trial comparing weekly paclitaxel (80 mg/m<sup>2</sup>) vs. 3-weekly paclitaxel (180 mg/m<sup>2</sup>) combined with carboplatin (area under the curve [AUC] 6 mg/mL/min) in stage II–IV epithelial ovarian carcinoma (EOC) [5]. Median PFS was superior in the weekly compared with the 3-weekly treatment group (28.0 vs. 17.2 months; hazard ratio [HR]=0.71; 95% confidence interval [CI]=0.58–0.88; p=0.0015). Three-year OS was also higher in the dose dense paclitaxel group (72.1% vs. 65.1%; HR=0.75; 95% CI=0.57–0.98; p=0.03). Notably, no significant difference in the response rate between 3-weekly and weekly paclitaxel was observed.

Following the positive PFS and OS benefits of the JGOG 3016 study, the GOG group (GOG 262) ran a similar trial comparing weekly paclitaxel (80 mg/m<sup>2</sup>) and 3-weekly paclitaxel (175 mg/m<sup>2</sup>) in combination with carboplatin (AUC 6 mg/mL/min), but permitted the addition of bevacizumab (15 mg/kg every 3 weeks) for patients in either arm of the study as well. In the intention to treat analysis, PFS was not prolonged when paclitaxel was administered weekly compared to 3 weekly (14.7 vs. 14.0 months; HR=0.89; 95% CI=0.74–1.06; p=0.18) [6]. In a subgroup analysis of patients who had not received bevacizumab, weekly paclitaxel significantly improved PFS by 3.9 months compared to 3-weekly paclitaxel. However, in the

**Table 1.** Summary of randomised phase 3 studies of weekly vs. 3 weekly paclitaxel

Study and phase	Population	No. of patients	Dose and schedule	Median PFS	Median OS	Response rate (%)
JGOG 3016	Stage II–IV EOC	637	(A) C AUC 6 D1, P 80 mg/m <sup>2</sup> over 1 hr D1, 8, 15 (B) C AUC 6 D1, P 180 mg/m <sup>2</sup> over 3 hr D1	28.2 m vs. 17.5 m (HR=0.76; p=0.0037)	Median OS 100.5 m vs. 62.2 m (HR=0.79; p=0.039)	Overall response rate 56% vs. 53% (p=0.72)
Katsumata et al. [5], phase III						
GOG 262	Untreated, incompletely resected stage III–IV EOC	692	(A) C AUC 6 D1, P 80 mg/m <sup>2</sup> D1, 8, 15, optional Bev 15 mg/kg	Received Bev: 14.9 m vs. 14.7 m (HR=0.99; p=0.60)	-	-
Chan et al. [6], phase III	Neoadjuvant–88 (13%)		(B) C AUC 6 D1, P 175 mg/m <sup>2</sup> D1, optional Bev 15 mg/kg	Did not receive Bev: 14.2 m vs. 10.3 m (HR=0.62; p=0.03)		
ICON8	FIGO IC–IV (high risk FIGO IC–IIA)	1,566	(A) C AUC 5 D1, P 175 mg/m <sup>2</sup> over 3 hr D1	24.4 m vs. 24.9 m vs. 25.3 m (HR=0.92 – arms B vs. A) (HR=0.94 – arms C vs. A)	-	-
Clamp et al. [16], phase III (abstract form)	Predominantly European		(B) C AUC 5, P 80 mg/m <sup>2</sup> over 1 hr D1, 8, 15 (C) C AUC 2 D1, 8, 15, P 80 mg/m <sup>2</sup> over 1 hr D1, 8, 15			
GOG 252	FIGO II–IV	1,560	(A) IV weekly P 80 mg/m <sup>2</sup> , IV C AUC 6, IV Bev 15 mg/kg	24.9 m vs. 27.3 m vs. 26.0 m (HR=0.947; p=0.416 – arms B vs. A) (HR=1.01; p=0.727 – arms C vs. A)	-	-
Walker et al. [17], phase III (abstract form)			(B) IV weekly P 80 mg/m <sup>2</sup> , IP C AUC 6, IV Bev 15 mg/kg (C) IV P 135 mg/m <sup>2</sup> , IP Cisplatin 75 mg/m <sup>2</sup> , IP P 60 mg/m <sup>2</sup> , IV Bev 15 mg/kg			
MITO-7	FIGO IC–IV	822	(A) C AUC 6, P 175 mg/m <sup>2</sup> D1 (B) C AUC 2, P 60 mg/m <sup>2</sup> D1, 8, 15	17.3 m vs. 18.3 m (HR=0.96; p=0.66)	2-yr OS 78.9% vs. 77.3% (HR=1.2; p=0.22)	Objective response 58% vs. 56% (p=0.63)
Pignata et al. [15], phase III						

AUC, area under the curve (unit: mg/mL/min); Bev, bevacizumab; C, carboplatin; D, day; EOC, epithelial ovarian carcinoma; FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group; HR, hazard ratio; IP, intraperitoneal; JGOG, Japanese Gynaecologic Oncology Group; MITO, Multicenter Italian Trials in Ovarian cancer; OS, overall survival; P, paclitaxel; PFS, progression-free survival.

84% of patients who received bevacizumab, no improvement in PFS was seen, suggesting that the benefit of dose-dense weekly paclitaxel may only be observed in the absence of additional anti-angiogenic therapy in the adjuvant setting.

The Multicenter Italian Trials in Ovarian cancer study (MITO-7) was designed to establish superiority of weekly carboplatin (AUC 2 mg/mL/min) and paclitaxel (60 mg/m<sup>2</sup>) over carboplatin (AUC 6 mg/mL/min) plus paclitaxel (175 mg/m<sup>2</sup>) every 3 weeks for 6 cycles. The study did not demonstrate any significant PFS benefit (18.3 vs. 17.3 months; HR=0.96; 95% CI=0.80–1.16; p=0.66) for the weekly regimen over the 3 weekly regimen [15]. Of note however, unlike the JGOG 3016 and GOG 262 trials, the weekly dose of paclitaxel was lower, with carboplatin AUC 2 mg/mL/min and paclitaxel 60 mg/m<sup>2</sup> being administered every week for 18 weeks. Despite the lack of PFS benefit, the study found that fewer patients assigned to the weekly group had grade 3–4 neutropenia, febrile neutropenia, grade 3–4 thrombocytopenia and grade 2 or worse neuropathy, suggesting that the weekly MITO-7 regimen could be a good option in patients with poorer performance status or at higher risk of chemotherapy related infective complications.

The recent three arm ICON8 trial compared 6 cycles of 3-weekly carboplatin (AUC 5 mg/mL/min) and paclitaxel (175 mg/m<sup>2</sup>) with 3-weekly carboplatin plus weekly paclitaxel (80 mg/m<sup>2</sup>) and weekly carboplatin (AUC 2 mg/mL/min) and paclitaxel (80 mg/m<sup>2</sup>). Both weekly paclitaxel regimens were not found to be superior with PFS being similar in all arms at 24.4 vs. 24.9 vs. 25.3 months respectively. OS data is not mature [16].

GOG 252 enrolled 1,560 patients with stages II-IV epithelial ovarian, peritoneal, or fallopian tube carcinoma and randomized them to receive 6 cycles of chemotherapy in one of three arms. Chemotherapy comprised of either 1) carboplatin AUC 6 mg/mL/min and weekly paclitaxel 80 mg/m<sup>2</sup>, or 2) weekly paclitaxel 80 mg/m<sup>2</sup> with intraperitoneal carboplatin AUC 6 mg/mL/min, or 3) 3 weekly paclitaxel 135 mg/m<sup>2</sup> on day 1 with intraperitoneal cisplatin 75 mg/m<sup>2</sup> on day 2 and intraperitoneal paclitaxel 60 mg/m<sup>2</sup> on day 8. Patients in all arms also received bevacizumab from cycle 2 onwards, and continued with maintenance bevacizumab until cycle 22. The median PFS by intention to treat analysis was 24.9 months vs. 27.3 months vs. 26.0 months respectively. No significant PFS advantage was observed with the addition of intraperitoneal chemotherapy [17].

## QUALITY OF LIFE CONSIDERATIONS FOR WEEKLY VS. 3 WEEKLY PACLITAXEL

Quality of life (QoL) assessments were carried out in the JCOG 3016, GOG 262, and MITO-7 studies.

In JCOG 3016, 30% of 631 patients completed quality of life (QoL) assessments at 12 months after randomization. Using a few Functional Assessment of Cancer Therapy (FACT) subscales, the overall QoL did not differ significantly with dose dense paclitaxel. However, according to the FACT-taxane (FACT-T) subscale, QoL was poorer in the dose dense group (p=0.02) [18].

FACT-ovarian, trial outcome index (FACT-O TOI) scores were lower in patients receiving dose dense paclitaxel in GOG 262, implying a perceived deterioration in QoL. In the MITO-7 trial, patients who received standard 3-weekly chemotherapy reported worsening FACT-O TOI

scores after each cycle, whereas among those receiving the weekly 60 mg/m<sup>2</sup> schedule, scores remained stable after a transient drop at week 1.

No significant difference has been observed in febrile neutropenia rates in JGOG 3016, although rates were significantly lower with MITO-7 where the weekly dose of paclitaxel was lower at 60 mg/m<sup>2</sup> (0.5% vs. 3%). However, the rate of grade 3 and higher anemia was significantly higher in both the JGOG 3016 (69% vs. 44%,  $p < 0.0001$ ) and GOG 262 (36% vs. 16%,  $p < 0.001$ ) trials. The ICON8 trial did report slightly increased grade 3 to 4 toxicities with weekly paclitaxel containing regimens, however this was attributed predominantly to uncomplicated hematological adverse events.

The incidence of paclitaxel induced peripheral neuropathy is more common with weekly than 3-weekly administration of paclitaxel, and is dependent on cumulative dose delivered, dose per cycle, and dose intensity [3,4]. This is a consistent finding across several trials including the phase III Cancer and Leukemia Group B (CALGB) 9840 breast cancer trial [19]. The rates of grade 2 and above sensory neuropathy was significantly higher in the dose dense arm of GOG 262 (26% vs. 18%,  $p = 0.01$ ). The incidence of neurotoxicity in JGOG 3016 (motor neuropathy 5% vs. 4%,  $p = 0.56$ , sensory neuropathy 7% vs. 6%,  $p = 0.87$ ) was similar between both administration schedules; however, this may be explained by the higher treatment discontinuation rate in the dose dense arm (38% vs. 27%).

Overall, the tolerability of the dose dense weekly regimen appears comparable to that of the conventional 3-weekly regimen, apart from increased rates of neuropathy and anemia seen in some the aforementioned studies with weekly paclitaxel at 80 mg/m<sup>2</sup>.

## WHAT ARE THE POSSIBLE REASONS FOR DIFFERENCES IN OUTCOMES IN JGOG 3016 VERSUS OTHER STUDIES?

### 1. Bevacizumab

Bevacizumab is a monoclonal antibody that disrupts angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A), which is involved in the progression of ovarian cancer [1]. Its synergistic effect with chemotherapy is demonstrated in the GOG 218, ICON7, OCEANS and AURELIA trials where the addition of bevacizumab significantly prolonged PFS and increased response rates [20-23]. As discussed earlier, the GOG 262 study illustrated that when patients were treated with front-line carboplatin, paclitaxel and bevacizumab, the dose dense schedule of paclitaxel administration was not superior for PFS. Notably however, in a subgroup analysis of patients who were not treated with bevacizumab in GOG 262, the weekly paclitaxel regimen was shown to improve progression-free survival compared with the 3-weekly regimen. One possible explanation for this observation is that the effect of PFS prolongation with dose dense weekly paclitaxel 80 mg/m<sup>2</sup> arm may be due to the enhanced anti-angiogenic effect of weekly paclitaxel, which is negated once bevacizumab is added to the 3-weekly carboplatin and paclitaxel regimen. This could also explain why no differences in PFS were observed in the GOG 252 study, where all patients also received bevacizumab.

In AURELIA, platinum resistant ovarian cancer patients were randomized to single agent chemotherapy with or without bevacizumab. The addition of bevacizumab improved PFS and objective response rate (ORR) significantly even in patients receiving weekly paclitaxel [23]. Of note, no difference in response rates between dose dense (71%) and 3 weekly

paclitaxel (70%) regimens were seen in JGOG 3016 [5]. The reasons as to why improvements in outcomes when bevacizumab is combined with weekly paclitaxel have been demonstrated in the platinum resistant (AURELIA) setting, but not in the first line (GOG 262) remain unknown. One possible explanation is that anti-angiogenic therapy has a greater impact on the molecular and microenvironmental characteristics of platinum resistant tumors, leading to increased efficacy when combined with chemotherapy in this context.

## 2. Relevance of histological and molecular subtypes of EOC and outcomes following dose dense paclitaxel

Ovarian cancer is a heterogeneous disease with several distinct histological subtypes. Traditionally, the five main carcinoma subtypes are high grade serous, endometrioid, clear cell, mucinous, low-grade serous carcinoma. These discrete subtypes have differing clinical features, chemotherapeutic response, and patient prognosis [24]. Clear cell and mucinous ovarian cancers are generally chemo-resistant compared to the serous subtypes. In JGOG 3016, PFS benefit was observed mainly in the high grade serous subtype, while increasing the dose density and intensity of paclitaxel did not seem sufficient to overcome the chemo-resistance of clear cell and mucinous ovarian cancers [5].

In recent years, efforts have been made to identify specific molecular subtypes of ovarian carcinomas which may respond better to chemotherapeutic agents. Tan et al. [25] identified five molecular subtypes (Epi-A, Epi-B, Mes, Stem-A, and Stem-B) of ovarian cancer, of which Stem-A represented a poorer prognostic group, yet exhibited elevated microtubule activity which rendered it sensitive to microtubule polymerization inhibitor drugs such as vincristine and vinorelbine.

The Australian Ovarian Cancer Study (AOCS) and TCGA have also identified four gene expression subtypes of high grade serous ovarian carcinoma (HGSOC) (C1/Mesenchymal, C2/Immunoreactive, C4/Differentiated, and C5/Proliferative) with differing prognostic implications [26]. These subtypes were not prognostically different in the original TCGA data set. However, when applied to a cohort of 174 HGSOCs from the Mayo Clinic, significant differences in OS were observed between the 4 subtypes. The C1/Mesenchymal subtype had the poorest median survival of 26.3 months, followed by the C5/Proliferative subtype (29.0 months). C2/Immunoreactive and C4/Differentiated subtypes had better prognosis with median survival times of 46.4 months and 42.1 months respectively [27].

Murakami et al studied these gene expression subtypes with an aim to determine response and resistance signatures to taxane- and platinum-based chemotherapy. Discriminative metrics were utilized to correlate with response signatures to carboplatin (C score) and to paclitaxel (T score). While C scores were significantly lower in the C1/Mesenchymal subtype ( $p < 0.0001$ ), T scores were significantly higher in this subtype compared to the others ( $p < 0.0001$ ). These results are concordant with prior reports that the C1/Mesenchymal subtype may be resistant to platinum chemotherapy, but more sensitive to taxanes [28].

Furthermore, Kommoss et al. [29] recently reported that the C1/Mesenchymal and C5/Proliferative subtypes also appear to benefit more when exposed to bevacizumab. Gene expression analysis was performed on archival tumors from patient cohorts of the AGO-OVAR11 group in the ICON7 trial. PFS prolongation was found to be greater in the angiogenic driven C5/Proliferative (10.1 months) and C1/Mesenchymal subtypes (8.2 months), compared to the C2/Immunoreactive (3.8 months) or C4/Differentiated (3.7 months) subtypes with bevacizumab [29].



Murakami et al. [30] also developed new pathologic classifications of high grade serous ovarian cancer based on gene expression microarray data (Mesenchymal Transition type, Immune Reactive type, Solid and Proliferative type, and Papillo-Glandular type). These subtypes correlate with the previously defined TCGA gene expression subtypes. The Mesenchymal Transition type had the poorest overall survival, but nonetheless had comparable PFS with the Solid and Proliferative and Papillo-Glandular subtypes. Response to chemotherapy in each of these subtypes was analyzed using a gene expression microarray data set derived from laparoscopic biopsy specimens obtained from patients who were subsequently treated with paclitaxel or carboplatin monotherapy. Patients with Mesenchymal Transition type had better PFS and OS when treated with taxane containing regimens compared with non-taxane regimens. Subsequently, the same group retrieved 207 high grade serous ovarian cancer slides from the JGOG 3016 study and classified the samples into these 4 subtypes. The Mesenchymal transition subtype was the only group with significantly better median survival when treated with carboplatin and dose dense paclitaxel compared to standard 3 weekly paclitaxel and carboplatin (1.8 vs. 1.2 years,  $p=0.01$ ) [31].

It is possible that the prevalence of the C1/Mesenchymal subtype is higher within the Japanese cohort studied in JGOG 3016 compared to the Caucasian majority population in the aforementioned western-based trials. This could potentially explain the differing outcomes of dose dense weekly paclitaxel seen in JGOG 3016 compared with GOG 262/252 and ICON8. Alternatively, it could also be the case that there was an imbalance between the C1/Mesenchymal in the weekly vs. 3 weekly paclitaxel arms for GOG 262, ICON8 and GOG 252 such that the beneficial effect of dose-paclitaxel in this particular molecular subgroup could have been diluted. This could have been further confounded by the addition of bevacizumab in GOG 262 and GOG 252 which, as reported by Kommoss et al. [29], would have potentially resulted in increased the PFS for patients with the C1/mesenchymal and C5/proliferative molecular subtypes of ovarian carcinoma. Likewise, there is evidence to suggest bevacizumab may also have a negative impact on certain immunogenic molecular subgroups of ovarian carcinoma which could also have affected the PFS results in these studies [32]. Post-hoc analysis of these gene expression subtypes in completed studies may help to determine the predictive value of molecular subtyping and provide the basis for future molecular-subtype stratified trial designs for studies incorporating dose dense paclitaxel chemotherapy.

### 3. *BRCA1/2* mutation status

The association between *BRCA1/2* mutations and decreased sensitivity to taxanes has been reported. Quinn et al. [33] demonstrated that higher *BRCA1* expression in ovarian cancer correlated with improvement in OS following taxane containing chemotherapy (23.0 months vs. 18.3 months,  $p=0.12$ ), suggesting that patients with *BRCA1* wild-type genes, and hence higher *BRCA1* expression, would have better clinical responses to taxanes. However, conflicting data exists, Tan et al. [34] studied 26 *BRCA* mutated ovarian cancer patients receiving paclitaxel monotherapy for relapsed disease and concluded that paclitaxel is an active treatment option with a response rate of 46%, and that the clinical benefit rate was superior in platinum sensitive compared with platinum resistant patients. The same retrospective study also observed that in platinum resistant patients, response rate was higher when treated with weekly paclitaxel (33%) than 3 weekly paclitaxel (0%). Perhaps differences in the numbers of *BRCA* mutated or other homozygous recombinant DNA repair deficient patients may have contributed to varying PFS and OS observed in previously conducted trials.

The proportion of *BRCA* mutations differ among the various ethnicities, with the highest prevalence among Africans and lowest in women from the Middle East [35]. Sakamoto et al. [36]

analyzed 95 unselected ovarian cancer cases and evaluated for germline *BRCA 1/2* gene mutations with next generation sequencing (NGS) and found deleterious mutations in 12.6% of patients, which is similar to the 14% rate of germline *BRCA1/2* mutations reported in caucasian populations [37]. Further analysis of the outcomes of patients with germline and somatic *BRCA* mutations in completed studies should also be performed to help resolve this issue.

#### 4. Biological and ethnic differences, and the pharmacogenetics of paclitaxel

It has been suggested that the difference in outcome between JGOG and the other studies were due to pharmacogenetics differences in Japanese versus Western populations.

Among patients who receive paclitaxel, a proportion experience therapeutic efficacy with minimal side effects, while some suffer toxicities while having minimal response. Paclitaxel efficacy and toxicity are determined by drug exposure, and genetic variations may contribute to the variability of paclitaxel pharmacokinetics and pharmacodynamics [38]. There are ethnic differences in genotypic distribution of genes involved in the metabolism of paclitaxel [39]. The cytochrome P450 enzymes (CYP450) are crucial in the metabolism of many medications, including chemotherapy. Within the hepatocyte, paclitaxel undergoes CYP2C8 and CYP3A4/5 mediated metabolism to 6 $\alpha$ -hydroxypaclitaxel and p-3'-hydroxypaclitaxel respectively.

The CYP2C8\*3 enzymatic variant is associated with decreased metabolism of paclitaxel. Patients carrying this variant allele may experience higher therapeutic drug exposure. This variant is more commonly seen in the Caucasian population (9%–15%) compared to in the Japanese (<1%) [39]. This should theoretically confer superior exposure and hence response and outcome in Caucasian compared with Japanese patients treated with dose dense paclitaxel, however trial data revealed the opposite. One possible explanation is that the role of CYP2C8\*3 may be counterbalanced by variations in other enzyme systems involved in paclitaxel metabolism. In the CYP3A enzymatic system, the CYP3A5 allele is usually non-functional in Caucasian patients. Functional CYP3A5 alleles, which exist due to the g.6986A variant allowing for normal splicing of transcripts, have frequencies of 5% in Caucasians, 29% in Japanese, and 73% in African-Americans [40]. Functional alleles possibly increase CYP3A5 activity and resulting in greater paclitaxel clearance and reduced toxicities.

The exact role and clinical impact of these pharmacogenetic ethnic variations have yet to be clearly elucidated [41], but nonetheless suggest that there may be other yet unknown pharmacokinetic factors that could lead to differences in outcome between different ethnic groups exposed to the same therapeutic dose and regimen of drug. Further research in this area is certainly warranted.

## CONCLUSIONS

To date, only the JGOG 3016 study has been shown to be positive for improved outcomes following dose dense paclitaxel chemotherapy. Despite similar tolerability when compared to the 3-weekly regimen, weekly administration of paclitaxel at the dose of 80 mg/m<sup>2</sup> is associated with increased risks of anemia and neurotoxicity [5].

It is also increasingly clear that ovarian cancer is a histologically and molecularly heterogenous disease. In JGOG 3016, despite the overall positive increase in PFS and OS, certain histological subtypes, such as those with clear cell or mucinous histology did not



benefit from the dose dense schedule [5].<sup>5</sup> Moreover the 4 different gene expression subtypes of high grade serous ovarian carcinomas are associated with differing resistance and response signals to platinum and taxane chemotherapy and may have affected the outcomes of the aforementioned trials [28]. Of note, the C1/Mesenchymal subtype had the best response to paclitaxel, but was also the most resistant to carboplatin [28]. The C1/Mesenchymal and C5/Proliferative subtypes are more pro-angiogenic and seem to derive progression free survival benefit from the addition of bevacizumab to both 3-weekly or weekly paclitaxel containing chemotherapy [29].

Given that four out of five randomized studies have shown no benefit of dose dense paclitaxel in terms of PFS (GOG 262, MITO-7, GOG 252, ICON8) and OS (MITO-7), it would appear that paclitaxel administered in combination with carboplatin at 3-weekly intervals remains the standard of care for women with advanced ovarian carcinoma [6,15-17]. Nonetheless, the results of the JGOG 3016 cannot be ignored, and it would certainly be reasonable to discuss both the dose dense weekly and 3-weekly paclitaxel regimens with patients when considering adjuvant therapy for advanced ovarian carcinoma, particularly in patients of Japanese descent with high grade serous carcinoma.

In the meantime, it is envisaged that an improved understanding of the distinct pharmacogenetic variations between Caucasian and Japanese ethnic groups, and their functional relevance to paclitaxel pharmacokinetics and pharmacodynamics, may eventually help to explain the difference in survival benefit observed between JGOG 3016 and other trials of weekly and dose dense paclitaxel in Caucasian dominant study populations. If validated, the consideration of these potential clinical and biological factors will be essential for future prospective trials incorporating patients from different ethnic backgrounds.

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