



What is the impact of dose modification in adjuvant chemotherapy for ovarian cancer?

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Ovarian cancer is the eight most common cancer occurring in women worldwide (1). The cornerstone of management of advanced epithelial ovarian cancer (EOC) and primary peritoneal carcinoma (PPC) involves primary debulking surgery followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by interval cytoreduction (2,3). The chemotherapy backbone remains as carboplatin and paclitaxel. Although several trials have tried to improve outcomes by incorporating additional chemotherapy agents this has not proved successful. Dose modifications with carboplatin and paclitaxel are relatively common, with haematological and neurological toxicities experienced by many patients. The impact chemotherapy dose modifications have on patient outcomes in advanced EOC have been evaluated in single centre retrospective studies; with results to date suggesting reduced relative dose intensity (RDI) confers inferior outcomes (4,5). Five-year survival for EOC has improved since the 1980s from <40% to 45 (6). However, overall outcomes remain poor due to high rates of recurrent disease and advanced disease stage at presentation. This then raises the question of how this can be improved, in particular would greater dose intensity in the adjuvant setting be of value.

Olawaiye *et al.* (7) reported in *Gynecologic Oncology* in October 2018 on a retrospective analysis of 738 patients with FIGO stage III or IV EOC or PPC treated on the control arm of the GOG-182 trial completing eight cycles of intravenous chemotherapy [three-weekly carboplatin, area under the curve (AUC) of 6 and paclitaxel at 175 mg/m²] with or without dose modification. The GOG-182 trial (8) was a five-arm randomized, multicentre

trial of carboplatin and paclitaxel versus combinations with gemcitabine, pegylated-liposomal doxorubicin or topotecan including triplet therapy. Patients were stratified by group, diagnosis (EOC *vs.* PPC), FIGO stage (III *vs.* IV), macroscopic residual disease and intent for interval cytoreduction (yes or no). Dose modification was defined as chemotherapy dose reduction (of $\geq 15\%$ of cycle 1 dose) or cycle delay (of ≥ 3 weeks) or both. Sixty-nine percent of patient did not have a dose modification. There was a higher proportion of patients in the dose modified group who had stage IV (20.5% *vs.* 14.9%; $P=0.059$) and/or suboptimally debulked disease (31.4% *vs.* 26.7%; $P=0.365$), which are key prognostic features for high risk of relapse (9,10). The number of patients with normal performance status was lower in the dose modified group with 43% versus 54% in the non-dose modified group; $P=0.001$. There was increased use of growth factor support (G-CSF) in the dose modified group 40% compared with 24% in the non-dose modified group, $P<0.001$; though the use of G-CSF without dose modification was a protocol deviation. The median progression free survival (PFS) of the non-dose modified patients was significantly higher than the dose modified patients; 17.55 months (95% CI, 16.46–19.1 months) compared with 9.92 months (95% CI, 6.67–12.5 months), $P<0.001$. The median overall survival (OS) was 48 months (95% CI, 42.7–53.3 months) *vs.* 28.7 months (95% CI, 22.3–35.0 months), $P=0.021$ in the non-dose modified and dose modified patients respectively. The adjusted hazard ratio (HR) for disease progression in dose modified patients was 1.50 (95% CI, 1.27–1.78, $P<0.001$) and the adjusted HR for death in dose modified patients was 1.40 (95% CI,

1.17–1.68, $P < 0.001$). In clinical practice, patients have six cycles of carboplatin and paclitaxel and thus a multivariate analysis was performed limiting to the first six cycles of chemotherapy and revealed the HR for PFS and OS was the same as that reported for eight cycles; 1.50 (95% CI, 1.269–1.784; $P < 0.001$) and 1.40 (95% CI, 1.169–1.684; $P < 0.001$) respectively. This analysis demonstrates that dose modification results in worse PFS and OS in advanced EOC and PPC, however it should be noted that patients in this group had worse prognostic factors at presentation (i.e., poorer performance status, stage IV disease and suboptimally debulked) raising the question if this just reflects disease biology. The analysis does highlight the potential role that G-CSF could play in maintaining the RDI.

The concept of maintaining RDI was initially investigated in breast cancer and lymphoma trials revealing an RDI $< 85\%$ resulted in poorer patient outcomes (11,12). RDI is commonly defined as the amount of chemotherapeutic agent delivered compared to a standard dosing schedule over a specific time frame with a threshold of 85% commonly utilised in studies (13). Fauci *et al.* (5) conducted a retrospective analysis on 138 chemotherapy naïve patients treated with six cycles of a taxane and platinum in Stage I–IV EOC patients evaluating the impact of RDI. Sixty-nine percent of patients experienced at least one treatment delay or dose reduction during their treatment with the most common reason being thrombocytopenia (38%) and neutropenia (31%). Patients who achieved an RDI between 70% and 110% had a mean PFS of 32 months compared to 20 months in patients with an RDI of $< 70\%$ or $> 110\%$ ($P = 0.046$). The numbers of patients in group with an RDI $< 70\%$ or $> 110\%$ was small however demonstrated no extra benefit was achieved with an RDI $> 110\%$ compared with an RDI between 70% and 110%. Denduluri *et al.* (14) performed a retrospective cohort study in 170 advanced ovarian cancer patients to evaluate the association between RDI and OS. Dose delays and reductions were experienced by 43.5% and 48.2% respectively, and 46.5% had RDI $< 85\%$. In the multivariable Cox proportional hazards model, dose reductions $\geq 15\%$ (HR = 1.94; 95% CI, 1.09–3.46; $P = 0.025$) and other tumour histology (serous *vs.* non-serous adenocarcinoma; HR = 3.55; 95% CI, 1.38–9.09; $P = 0.008$) were significantly associated with mortality.

The multicenter, randomised ICON8 trial (15) assessed if increasing dose intensity either with dose dense or weekly carboplatin and paclitaxel would improve ovarian cancer patient outcomes based on findings from the JGOG3016 trial (16) in Japanese women. One thousand

five hundred and sixty-six women with FIGO stage Ic–IV disease were randomised to three arms; arm 1 being standard three weekly carboplatin and paclitaxel, arm 2 three weekly Carboplatin and dose-dense weekly paclitaxel and arm 3 weekly dosing of both carboplatin and paclitaxel. A higher proportion of patients completed 6 cycles in arm 1; 72% compared with 60% and 63% in arm 2 and 3 respectively. Patients in arm 2 experienced 63% grade 3/4 toxicity (predominantly uncomplicated neutropenia compared with 53% and 42% in arm 3 and 1 respectively. There was no improvement in PFS noted with the weekly or dose dense arms when compared with the standard three weekly carboplatin and paclitaxel schedule (log-rank arm 2 *vs.* 1, $P = 0.45$; arm 3 *vs.* 1, $P = 0.56$, median PFS: 17.9, 20.6 and 21.1 months in arms 1, 2 and 3 respectively). The authors concluded that although weekly dose-dense chemotherapy can be delivered in this setting without a substantial increase in toxicity, this does not significantly improve PFS.

A retrospective analysis (17) of 552 EOC patients in the Ovarian cancer Prognosis And Lifestyle (OPAL) study, an Australian prospective study was performed to determine the impact chemotherapy dose modifications have on patient outcomes in the adjuvant setting. Patients were identified from the databases commencing either three-weekly carboplatin (AUC 5/6) and paclitaxel 175 mg/m² or carboplatin (AUC 5/6) and weekly paclitaxel 80 mg/m². There was a higher proportion of all intended chemotherapy doses completed in the three-weekly cohort (77% *vs.* 45%; $P < 0.001$). The dose dense cohort experienced a significantly higher percent of treatment delays and reductions; 32% *vs.* 64% ($P < 0.001$) and 29% *vs.* 49% ($P < 0.001$) respectively. The median PFS however was not impacted by dose reduction or dose delays in either treatment groups.

Banerjee *et al.* (18) evaluated the impact of intra-patient carboplatin dose-escalation *vs.* standard flat dosing on patient outcomes in a phase III, international multicentre prospective randomised trial involving 964 patients. Patients were randomised eight weeks postoperatively to either flat dose three-weekly carboplatin AUC 6 without dose escalation (arm A) or intra-patient dose escalation based on nadir blood count (arm B). Dose escalation was achieved in 77% of patients who had ≥ 1 cycle. However, there was a higher proportion of grade 3/4 non-haematological toxicity in the dose escalation arm B (31% *vs.* 22%, $P = 0.001$). The median PFS was 12.1 months in arm A and B (HR 0.99; 95% CI, 0.85–1.15; $P = 0.93$). The median OS was 34.1 and 30.7 months in arms A and B, respectively (HR 0.98;

95% CI, 0.81–1.18, $P=0.82$). The study demonstrated that even though intra-patient dose escalation of carboplatin is possible this did not improve patient outcome. ICON8 (15) and SCOTROC-4 (18) highlight that escalating treatment dose intensity in ovarian cancer has not achieved a similar impact on patient outcomes as seen in breast cancer or lymphoma clinical trials (11,12). This is further supported by a recent meta-analysis performed by Marchetti *et al.* (19) where four randomised controlled trials comprising 3,689 eligible patients revealed no significant benefit on PFS (HR 0.92, 95% CI, 0.81–1.04, $P=0.20$) by giving dose dense chemotherapy dosing reflecting that the three weeklies schedules remain standard of care.

Obesity, advanced age and poor performance status have been identified as predictors for women receiving reduced RDI. Dose modifications are common in obese patients, due to the risk of potential chemotherapy toxicity from over-dosing with body surface area (BSA) $>2.0 \text{ m}^2$. Hanna *et al.* (20) performed a multicenter, retrospective study on 325 women with FIGO stage III–IV EOC evaluating only the first four cycles of adjuvant chemotherapy of varying treatment schedules and agents. Ninety percent of patients had a BSA $<2.0 \text{ m}^2$ and 88.9% of patients were treated with a carboplatin containing regimen. Logistic regression analysis revealed predictors of reduced planned RDI of $<85\%$ were treatment off a research protocol [odds ratio (OR) =4.30; 95% CI, 2.05–9.02] and BSA $>2.0 \text{ m}^2$ (OR =6.14; 95% CI, 2.32–16.20). Predictors of reduced RDI being actually delivered were body mass index (BMI) $>30 \text{ kg/m}^2$ (OR =2.35; 95% CI, 1.25–4.41) and use of carboplatin (OR =2.71; 95% CI, 1.30–5.64). In the multivariate regression analysis, suboptimal tumour debulking was associated with lower PFS (HR 2.0; 95% CI, 1.06–3.79). Elevated cycle 1 Ca125 (HR 2.29; 95% CI, 1.16–4.53) and delivered RDI $<85\%$ (HR 1.71; 95% CI, 1.19–2.45) were independently associated with lower OS.

This is further supported by a retrospective analysis performed by Au-Yeung *et al.* (21) of 333 patients with FIGO stage III–IV EOC undergoing adjuvant carboplatin AUC 5 and paclitaxel 175 mg/m^2 to evaluate the relationship between BMI, RDI and patient outcomes. More patients in the obese group received under-dosing of carboplatin compared to the normal and over-weight group resulting in higher proportion of obese patients receiving an RDI $<85\%$ compared to non-obese patients ($P<0.001$). Patients receiving RDI $<85\%$ for carboplatin were more likely to have a poorer PFS compared to patients receiving RDI $\geq 85\%$ (HR 1.29, $P=0.04$). Median PFS

for those receiving RDI $<85\%$ was 11 months, compared to 15 months for those receiving RDI $>85\%$. These two retrospective studies demonstrate the potential impact that dose modifications have on obese patient outcomes. This may more commonly happen in the dosing of obese patients, due to the potential inaccuracies of formulas used to calculate the glomerular filtration rate such as Cockcroft Gault (GFR). Hence, we recommend that a nuclear GFR scan is used to guide optimal carboplatin dosing in the adjuvant therapy of ovarian cancer, particularly in settings where a calculated GFR is more likely to be inaccurate such as older patients with impaired renal function or those at the extremes of body size (22).

Patients >70 years of age are generally a small population within clinical trials and thus it is hard to extrapolate findings to day-to-day practice. In a further analysis of the GOG-182 trial, Tew *et al.* (23) evaluated the outcomes and toxicity differences in 620 patients who were ≥ 70 years, which accounted for 16.8% of the eligible patients. Thirty six percent of older patients on the control arm (carboplatin and paclitaxel) reported \geq grade 2 peripheral neuropathy compared with 20% in younger patients and had a lower completion rates of all 8 cycles (72% *vs.* 82%, $P<0.001$). The median progression free interval was similar between older and younger patients with 15 *vs.* 16 months ($P=0.015$). However median OS was shorter at 37 *vs.* 45 months ($P<0.001$), respectively. The incidence of ovarian cancer increases with older age and thus the optimal chemotherapy dosing in older patients to minimise toxicity and improve patient outcomes is a key clinical question that still remains to be addressed. The currently recruiting EWOC-1 multicentre, randomised clinical trial (24) aims to answer this pertinent clinical question by exploring different dose schedules of Carboplatin and Paclitaxel in patients >70 years with a geriatric vulnerability score >3 . This group is defined as patients at high risk of severe toxicity, early cessation of treatment, unplanned hospitalisation and adverse outcomes based on poor survival risk factors [Activities of Daily Living (ADL) score <6 , Instrumental Activities of Daily Living (IADL) score <25 , Hospital Anxiety and Depression Scale (HADS) score >14 , albuminaemia $<35 \text{ g/L}$ and, lymphopenia $<1 \text{ g/L}$]. The trial will compare the standard three-weekly carboplatin and paclitaxel with single-agent carboplatin treatment as well as weekly dosing of both carboplatin and paclitaxel. The primary outcome is the success rate of delivering six cycles of chemotherapy with evidence of efficacy and without premature termination for progression, death

or unacceptable toxicity. This will be an important study given that many patients we see are elderly. In a previous publication from the Australian Ovarian Cancer Study cohort, only half of 1,192 patients completed 6 cycles of adjuvant chemotherapy without treatment modification or delay, and advanced age was the strongest predictor of not completing the planned treatment (25). Within the Australian New Zealand Gynaecological Oncology Group (ANZGOG) we are currently conducting a randomized phase III clinical trial called ECHO to determine if the addition of a structured exercise intervention during adjuvant chemotherapy will help reduce the toxicity of chemotherapy and actually improve chemotherapy completion rates (ACTRN12614001311640).

In clinical practice, patients are commonly faced with haematological and neurological toxicities and as clinicians we need to determine the optimal dosing to minimize toxicity. Whilst prophylactic G-CSF helps minimise haematological toxicities mainly neutropenia; this would not minimise risk of thrombocytopenia or dose reductions due to taxane related neuropathy. Olawaiye *et al.* (7) raises an important clinical consideration regarding the use of prophylactic G-CSF where feasible to maintain dose intensity and minimise dose modifications to give patients with advanced EOC and PPC the best possible outcome. Whilst studies to date have been largely retrospective, these do suggest an adverse impact with delivering a lower RDI of adjuvant chemotherapy to ovarian cancer patients. However, data from future prospective clinical trials are needed in order to definitely answer this clinical question. Based on the available evidence to date, it is recommended that we continue to use standard 3 weekly carboplatin and paclitaxel chemotherapy, as well as carefully optimize patient dosing in order to achieve optimal outcomes for our patients.

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