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Dose-dense weekly chemotherapy in advanced ovarian cancer: An updated meta-analysis of randomized controlled trials

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ABSTRACT

Objective: The use of dose-dense weekly chemotherapy in the management of advanced ovarian cancer (OC) remains controversial. The aim of this meta-analysis was to evaluate the efficacy of dose-dense regimen to improve clinical outcomes in OC patients with the inclusion of new trials.

Methods: For this updated meta-analysis, PubMed Medline and Scopus databases and meeting proceedings were searched for eligible studies with the limitation of randomized controlled trials, comparing dose-dense chemotherapy versus standard treatment. Trials were grouped in two types of dose-dense chemotherapy: weekly dose-dense (both paclitaxel and carboplatin weekly administration) and semi-weekly dose-dense (weekly paclitaxel and three weekly carboplatin administration). Data were extracted independently and were analyzed using RevMan statistical software version 5.3 (http://www.cochrane.org). Primary end-point was progression-free survival (PFS).

Results: Four randomized controlled trials comprising 3698 patients were identified as eligible. Dose-dense chemotherapy had not a significant benefit on PFS (HR 0.92, 95% CI 0.81–1.04, p = 0.20). When the analysis was restricted to both weekly and semi-weekly dose-dense data, a no significant interaction between dose-dense and standard regimen was confirmed (HR 1.01, 95% CI 0.93–1.10 and HR 0.82, 95% CI 0.63–1.08, respectively).

Conclusions: In the absence of PFS superiority of dose-dense schedule, three weekly schedule should remain the standard of care for advanced OC.

1. Introduction

Ovarian cancer (OC) represents, for incidence, the sixth most common cancer worldwide, and it is characterized by poor prognosis (Torre et al., 2016). Intravenous 3-weekly carboplatin and paclitaxel remain the standard chemotherapy drugs for first-line therapy in advanced OC, after complete cytoreductive surgery is achieved (Anon., 2017a). Over the ears, modifications in adjuvant chemotherapy regimen, including dose-dense schedules, have been investigated in different trials and provided conflicting results regarding clinical outcomes and toxicity. More recently, at the 5th Consensus Conference on Ovarian Cancer, the administration of weekly intravenous paclitaxel has been established as an acceptable alternative to three weekly intravenous paclitaxel in combination with 3-weekly intravenous carboplatin (Karam et al., 2017). With this regard, in our previous meta-analysis – based on 3 randomized trials – we showed that dose-dense chemotherapy is associated with improved progression-free survival (PFS) when compared with standard three weeks scheme (Marchetti et al., 2016). Nonetheless, because results from the largest randomized study on this topic (Clamp et al., 2017) has been presented since the original publication of previous meta-analysis, we provide an update, aiming to confirm or not the superiority of dose-dense chemotherapy over the standard regimen.

2. Methods

2.1. Data extraction and trials selection

The method was similar to our previous publication (Marchetti et al., 2016). We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to perform search strategy and selection processes. To reduce publication bias, data from

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all clinical randomized trials, both abstract and full-text paper, were included using literature electronic databases searching (Pubmed, Medline and Scopus) and hand searching (meeting proceedings of European Society of Medical Oncology and American Society of Clinical Oncology). The search term used were “randomized”, “dose-dense”, “paclitaxel”, “carboplatin”, “weekly” and “ovarian cancer” in the title. Randomized clinical trials, written in English, were included, without any restrictions on publication date. The last search was carried out on October 2017. To be eligible, clinical randomized trials had to compare carboplatin plus weekly paclitaxel with standard schedule of carboplatin plus paclitaxel every 3 weeks. Eligible trials had to include patients with non-metastatic histologically or cytologically proven epithelial ovarian, fallopian tube, or primary peritoneal cancer undergoing adjuvant chemotherapy curative treatment. Update published follow-up data were considered. Data collected included first author’s surname, year of publication, trial acronym, sample size of weekly and 3 weeks group, chemotherapy regimen, drug and dosage.

2.2. Endpoints

The primary endpoint was PFS, defined as the time from the date of randomization to last follow-up, death or disease progression. The hazard ratio (HR) and the number of events (death and progression), when available, were derived from each study. Secondary endpoint was severe acute toxicity. At least one of these two clinical outcomes should have been assessed and reported in the trial to be included in the analysis. Among trials reporting the results of different therapeutic approaches, when possible, we selected and included in a subgroup analysis only the groups of patients who underwent similar strategies.

2.3. Statistical analysis

Statistical analysis was performed using Review Manager version 5.3 (http://www.cochrane.org). We calculated the pooled HR with 95% confidence intervals (CIs) using a random-effects model. Forest plots were used for graphical representation of each study and pooled analysis. The size of each box represents the weight that the corresponding study exerts in the meta-analysis; CIs for each study are displayed as a horizontal line through the box. The pooled HR is symbolized by a solid diamond at the bottom of the forest plot, and the width of the square represents the 95% CI of the HR. HR, variance, 95% CI, log [risk ratio] and standard error for each study were extracted or calculated, based on the published studies, according to the methods described by Tierney et al. in 2007 (Tierney et al., 2007). A significant two-way p value for comparison was defined as $p < 0.05$. The Cochrane Q statistic (significant at $p < 0.1$) and the I^2 value (significant heterogeneity if > 50%) were used to examine the statistical heterogeneity among studies (Higgins et al., 2003). Publication bias was investigated using analyses described by Egger et al. (Egger et al., 1997) and Begg et al. (Begg and Mazumdar, 1994).

3. Results

3.1. Search results

One new randomized clinical trial, which included two relevant comparisons, was identified and included in the meta-analysis (Clamp et al., 2017). In total, four randomized phase III trials representing 3699 patients were eligible (Clamp et al., 2017; Katsumata et al., 2013; Pignata et al., 2014; Chan et al., 2016). Two trials were undertaken in Europe, one in USA and one in Japan. Interestingly, in Gynecologic Oncology Group (GOG) 0262 trial, patients in either group could opt to receive bevacizumab (Chan et al., 2016). Main characteristics of these trials are shown in Table 1. Globally, the control group – carboplatin AUC 5-6 plus paclitaxel 175–180 mg/m^2 every 3 weeks – rose to 1591 patients. Trials were also grouped according to the type of dose-dense used: weekly dose-dense, which used both paclitaxel and carboplatin weekly administration (Clamp et al., 2017; Pignata et al., 2014); semi-weekly dose-dense, in which paclitaxel was infused weekly but the carboplatin administration was unchanged compared with the reference group (Clamp et al., 2017; Katsumata et al., 2013; Chan et al., 2016).

3.2. Global analysis

All 3698 patients were included in this analysis. Compared with three-weekly regimen, dose-dense chemotherapy had not a significant benefit on PFS (HR 0.92, 95% CI 0.81-1.04, $p = 0.20$). Details are presented in Fig. 1. The OS analysis was not performed due to ICON8 immature data (350/602 events required) (Clamp et al., 2017).

3.3. Weekly dose-dense analysis

Two trials and 1853 patients were included in the weekly dose-dense analysis (Clamp et al., 2017; Pignata et al., 2014). In total, 1117 PFS events occurred. Weekly dose-dense regimen – carboplatin AUC 2 plus paclitaxel 60–80 mg/m^2 every week – was not associated with a significant benefit compared with standard three weekly chemotherapy (HR 1.01, 95% CI 0.93–1.10). Heterogeneity between trials was not significant ($p = 0.52$, $I^2 = 0\%$) (Fig. 2).

3.4. Semi-weekly dose-dense analysis

Three trials were included in the subgroup analysis of semi-weekly dose-dense chemotherapy versus standard scheme. The semi-weekly dose-dense regimen in the investigational arms was carboplatin AUC 5–6 every 3 weeks and paclitaxel 80 mg/m^2 every week. To minimize bias, considering that the GOG 0262 study design (Chan et al., 2016) provided bevacizumab to each patient who chose to receive it, we decided to include only data from the subgroup of patients who elected to not receive bevacizumab (n = 112). Thus, PFS subgroup analysis concerned data from GOG 0262 study without bevacizumab. In total 1787 patients were included in the PFS comparison. The effect of semi-weekly dose-dense chemotherapy was not significant on PFS (HR 0.82, 95% CI 0.63-1.08, $p = 0.17$) (Fig. 3).

3.5. Severe acute toxicity analysis

Only severe anemia and febrile neutropenia data were available for all four trials and thus only these toxicities were analyzed. Globally, severe acute anemia was significantly increased in patients treated with dose-dense chemotherapy (OR 1.95, 95% CI 1.13–3.34, $p = 0.02$; I^2 86%, $p = 0.0001$). The exclusion of the trial including bevacizumab (Chan et al., 2016) and the weekly dose-dense regimen (Clamp et al., 2017; Pignata et al., 2014) removed heterogeneity ($p = 0.96$, $I^2 = 0\%$), without modifying the significantly increased prevalence of severe acute anemia (OR 2.89, 95% CI 2.21–3.78) for patients treated with semi-weekly dose-dense chemotherapy compared with those given standard three weekly regimen (Fig. 4).

4. Discussion

This updated meta-analysis was performed to compare the efficacy of dose-dense versus three-weekly schedule in adjuvant chemotherapy for OC patients. Updated results did not confirm the effectiveness of dose-dense chemotherapy over standard treatment chemotherapy. In fact, there was no significant increase in PFS, although globally a higher proportion of events was recorded in patients treated with conventional chemotherapy. The peculiarity of the last trial included in this updated meta-analysis was the inclusion of two experimental arms −weekly dose-dense and semi-weekly dose-dense –, allowing to perform analyses with adequate power. When the analysis was restricted to single dose-