# Weekly paclitaxel with carboplatin in the first line treatment of advanced ovarian cancer

The JGOG3016 study [1, 2] indicated a relevant benefit in terms of both progression-free survival (PFS) and overall survival (OS) for a dose-dense regimen with paclitaxel (80 mg/mq) every week plus carboplatin (area-under-the-curve [AUC] 6 mg/mL) every 3 weeks, in comparison with the standard regimen of paclitaxel plus carboplatin every 3 weeks. These results raised a renewed interest for the weekly administration of paclitaxel, a strategy supported by preclinical studies indicating increased cytotoxic activity associated with extended drug exposure, and by phase II trials showing promising efficacy in women with ovarian cancer. However, the recently published results of MITO-7 failed to confirm this benefit. MITO-7 compared carboplatin (AUC 6 mg/mL) and paclitaxel (175 mg/mq) every 3 weeks for six cycles with a weekly regimen of carboplatin (AUC 2 mg/mL) and paclitaxel (60 mg/mq) for 18 weeks [3]. A third study (GOG 262), only reported in abstract form [4], indicated a possible benefit for the weekly regimen (similar to that utilized in the JGOG3016 trial), but only in patients receiving chemotherapy without bevacizumab. The conflicting results are even more relevant when we consider toxicity and quality of life (QoL). In the JGOG3016 study, the frequency of grade 3-4 anaemia was higher in the dose-dense regimen group (69%) than in the conventional treatment group (44%), while the frequencies of other toxic effects were similar. MITO-7 reported a more favourable toxicity profile for the weekly regimen with less frequent grade 3-4 neutropenia (50% *vs* 42%), febrile neutropenia (3% *vs* 0.5%), grade 3-4 thrombocytopenia (7% *vs* 1%), grade 2 or higher neuropathy (17% *vs* 6%), and grade 2 hair loss (59% *vs* 29%). GOG 262 indicated increased anaemia (40.8% *vs* 15.7%) and sensory neuropathy (25.9% *vs* 17.8%), but less neutropenia (72% *vs* 83.1%) with the weekly regimen. Finally, and most importantly, in the JGOG3016 study, the overall QoL did not differ significantly between the two treatment groups, but QoL according to the taxane subscale was worse in patients treated with the dose-dense regimen (p=0.02) [5]. Conversely, MITO-7, which had QoL as a co-primary endpoint, demonstrated worsening of the FACT-O/TOI scores at each cycle for the three-weekly treatment, while FACT-O/TOI scores remained stable in the weekly regimen, after transient worsening at week 1. This observation led the authors to conclude that a weekly regimen of carboplatin and paclitaxel might be a reasonable option for first-line treatment of women with advanced ovarian cancer. No QoL data are so far available from GOG 262.

## How to explain these differences in terms of efficacy, toxicity and QoL?

These studies differ in some aspects which could possibly explain the differences in outcome observed.

1. Different paclitaxel dose (60 mg/mq in MITO-7 *vs* 80 mg/mq in JGOG3016 and GOG 262) and carboplatin schedule (weekly *vs* three-weekly): the weekly regimen in MITO-7 cannot be considered dose-dense but rather a fractionated schedule of the same total dose. While no direct comparisons exist be-

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tween the efficacy of these two doses, all phase II trials indicating promising efficacy in ovarian cancer utilized 80 mg/mq/weekly. It is, on the other hand, fair to conclude that the lower toxicity and better QoL observed with the weekly regimen in MITO-7 is related to the lower paclitaxel dose. However, the slightly worse adherence to planned treatment of women assigned to the weekly regimen indicates some problematic issues not being picked up by the method utilized to assess QoL, such as the disruption of daily life and inconvenience of frequent hospital accesses. Moreover, no clear evidence is available for enhanced activity of weekly carboplatin, which, in turn, may increase the likelihood of subsequent hypersensitivity reactions [6].

2. Different ethnicity: genetic polymorphisms may account for differences in drug metabolism and consequently in side effects and efficacy. A subgroup analysis in GOG218 indicated a better survival for Asian/pacific islanders compared to other races, after adjustment for age, stage, residual disease, performance status and histology (p=0.013). ICON 8 is an ongoing study which utilized the JGOG3016 regimen in a Caucasian population and will be crucial to address the relevance of ethnicity on efficacy and toxicity.

## So, can weekly paclitaxel plus carboplatin be considered a new standard of care?

**Not enough evidence in terms of toxicity and QoL:** if the lower toxicity and better QoL in MITO-7 is related to the lower paclitaxel dose, which is, in turn, responsible for the lack of improvement in PFS and OS, this schedule cannot be considered the new standard of care.

**Not enough evidence in terms of efficacy:** the improved efficacy shown in the JGOG3016 study needs to be confirmed in non-Asian patients. The regimen should be feasible and have a more acceptable toxicity profile to be adopted as the new standard of care. The ongoing ICON 8 study will hopefully solve these uncertainties if it succeeds in demonstrating improved survival with acceptable toxicity in a non-Asian population.

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