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Long-term results of a randomised phase III trial of weekly versus three-weekly paclitaxel/platinum induction therapy followed by standard or extended three-weekly paclitaxel/platinum in European patients with advanced epithelial ovarian cancer

M.E.L. van der Burg [a,1], W. Onstenk [a,1], I.A. Boere [a,*], M. Look [a], P.B. Ottevanger [b], D. de Gooyer [c], L.G.M. Kerkhofs [d], F.A.A. Valster [e], J.B. Ruit [f], A.G.P.M. van Reisen [g], S.H. Goey [h], A.M.E. van der Torren [i], D. ten Bokkel Huinink [j], T.C. Kok [k], J. Verweij [a], H.C. van Doorn [l]

[a] *Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands*
[b] *Department of Medical Oncology, Radboud University Medical Centre, Nijmegen, The Netherlands*
[c] *Department of Internal Medicine, Franciscus Hospital, Roosendaal, The Netherlands*
[d] *Department of Internal Medicine, Admiraal de Ruyter Hospital, Vlissingen, The Netherlands*
[e] *Department of Internal Medicine, Lievensberg Hospital, Bergen op Zoom, The Netherlands*
[f] *Department of Internal Medicine, Vlietland Hospital, Schiedam, The Netherlands*
[g] *Department of Internal Medicine, ZorgSaam Zeeuws-Vlaanderen, Terneuzen, The Netherlands*
[h] *Department of Internal Medicine, Tweesteden Hospital, Tilburg, The Netherlands*
[i] *Department of Internal Medicine, Groene Hart Hospital, Gouda, The Netherlands*
[j] *Department of Internal Medicine, Diakonessenhuis, Utrecht, The Netherlands*
[k] *Department of Internal Medicine, Maasstad Hospital, Rotterdam, The Netherlands*
[l] *Department of Gynecological Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands*

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Abstract ***Background:*** Weekly paclitaxel/carboplatin might improve survival in platinum-resistant epithelial ovarian cancer (EOC). We compared efficacy of first-line weekly to three-weekly paclitaxel/cis- or carboplatin (PCw and PC3w) induction therapy, followed by either three or six PC3w cycles.

* *Corresponding author:* Address: Department of Medical Oncology, Room He-122, Erasmus MC Cancer Institute, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 10 703 48 97; fax: +31 10 703 46 27.
E-mail address: i.boere@erasmusmc.nl (I.A. Boere).
[1] These authors contributed equally to this work.

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Weekly
Carboplatin
Cisplatin
Paclitaxel

Patients and methods: In this multicentre, randomised phase III trial with 2×2 design, patients with FIGO stage IIb–IV EOC were randomised to six cycles PCw (paclitaxel 90 mg/m^2, cisplatin 70 mg/m^2 or carboplatin AUC 4) or three cycles PC3w (paclitaxel 175 mg/m^2, cisplatin 75 mg/m^2 or carboplatin AUC 6), followed by either three or six cycles PC3w. Primary endpoints were progression free survival (PFS) and overall survival (OS). Secondary endpoints were response rate (RR) and toxicity.

Results: Of 267 eligible patients, 133 received PCw and 134 PC3w. The first 105 patients received cisplatin, after protocol amendment the subsequent 162 patients received carboplatin. Weekly cisplatin was less well tolerated than weekly carboplatin. All PC3w cycles were well tolerated. At the end of all treatments, RR was 90.8% with no differences between the treatment arms. After a follow-up of median 10.3 years (range 7.1–14.8), median PFS was 18.5 (95% confidence interval (CI) 15.9–21.0) months for PCw and 16.4 (95% CI 13.5–19.2) months for PC3w ($p = 0.78$). Median OS was 44.8 (95% CI 33.1–56.5) months for PCw and 41.1 (95% CI 34.4–47.7) months for PC3w ($p = 0.98$).

Conclusions: There was no benefit in terms of OS, PFS or RR for a weekly regimen nor for extended chemotherapy as first-line treatment for EOC in European patients.

1. Introduction

Three-weekly paclitaxel/carboplatin and optimal cytoreductive surgery is the current standard of care for patients with advanced EOC. However, despite high initial response rates (RR) of ~75%, median progression free survival (PFS) is 16–21 months, and median overall survival (OS) is 32–57 months [1–5]. Disappointingly, adding a third cytotoxic agent to three-weekly paclitaxel/carboplatin, did not improve PFS nor OS [6–10]. Only recent results showed that adding the VEGF inhibitor bevacizumab improved median PFS with 1.5–3.8 months [11,12].

An alternative approach to improve outcome is by intensifying treatment regimens, either by increasing the dose per cycle or by shortening the time-interval between dose administrations (dose-densification). Several randomised studies investigated the potential benefit of dose-dense platinum on outcome. Dose-dense weekly cisplatin 50–70 mg/m^2 in combination with etoposide, topotecan or paclitaxel showed high activity in patients with recurrent EOC, including platinum-resistant patients, with RR of 46–63%, PFS of 5–8 months and OS of 10–11 months [13–15]. We recently reported high activity of six cycles weekly paclitaxel/carboplatin induction therapy followed by six cycles three-weekly paclitaxel/carboplatin in recurrent EOC [16]. In platinum-resistant patients, the overall RR was 58%, median PFS 8 months and OS 15 months. In platinum-sensitive patients the RR was 76%, PFS 13 months and OS 26 months, which is comparable to results obtained with three-weekly paclitaxel/carboplatin or four-weekly pegylated liposomal doxorubicin/carboplatin [17].

As first-line treatment, the benefit of increased dose-density on outcome remains to be investigated. The Japanese Gynecologic Oncology Group (JGOG) study showed improved OS with dose-dense paclitaxel combined with three-weekly carboplatin [18,19]. In contrast the MITO-7 trial did not show any survival benefit for dose-dense weekly paclitaxel/carboplatin [20]. Here, we explored the efficacy and tolerability of dose-dense weekly paclitaxel/cis- or carboplatin (PCw) compared to three-weekly paclitaxel/cis- or carboplatin (PC3w) as induction treatment for advanced EOC. After optional interval debulking surgery (IDS), patients not progressing on induction chemotherapy were randomised a second time to standard three cycles PC3w or extended therapy with six cycles PC3w.

2. Patients and methods

2.1. Patient selection

Main inclusion criteria for this open-label, multicentre, randomised phase III study with 2×2 design were: histologically proven EOC – including fallopian tube cancer and primary peritoneal carcinoma-, FIGO stage IIb–IV, World Health Organisation (WHO) performance status $\leqslant 2$, and adequate bone marrow, renal, and liver functions. Prior treatment with chemotherapy or radiotherapy was not allowed. Patients with a peripheral neurotoxicity $>$ grade 1 were not eligible. Full in- and exclusion criteria are specified in Supplementary data 1. Patients were included from 30 centres throughout The Netherlands. All patients gave written informed consent. This study was conducted in agreement with the Helsinki declaration of 1996.

2.2. Randomisation and procedures

After primary debulking surgery, or after diagnosis if irresectable, patients were randomised twice in a 1:1 ratio: firstly, between six cycles PCw or three cycles PC3w induction therapy, and secondly, between standard