Paclitaxel and cisplatin were superior to cyclophosphamide and cisplatin for advanced ovarian cancer

McGuire WP, Hoskins WJ, Brady MF, et al. ***Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer.*** *N Engl J Med. 1996 Jan 4;334:1-6.*

Objective
To compare cyclophosphamide and cisplatin with paclitaxel and cisplatin in women with advanced ovarian cancer.

Design
Randomised controlled trial with median 37-month follow-up.

Setting
41 centres in the United States.

Patients
386 women (mean age 60 y) who had stage III or stage IV ovarian cancer. Inclusion criteria were residual disease after surgery (> 1 cm residual mass) or stage IV disease, no previous chemotherapy or radiation therapy, Gynecologic Oncology Group (GOG) performance status score of 0 to 2, leukocyte count ≥ 3000/mm^3, platelet count ≥ 100 000/mm^3, serum creatinine level ≤ 177 μmol/L, and serum bilirubin and serum aspartate aminotransferase levels no more than twice the upper limit of normal. Women had to enter the study within 6 weeks of surgery. Women with a history of cardiac arrhythmia were excluded. 385 women (99.7%) received at least 1 course of treatment.

Intervention
Women were allocated to standard therapy (intravenous cyclophosphamide, 750 mg/m^2 of body surface area, and cisplatin, 75 mg/m^2 intravenously, 1 mg/min every 3 weeks for a total of 6 courses) (n = 202) or to experimental therapy (intravenous paclitaxel, 135 mg/m^2 as a 24-hr infusion, and cisplatin, 75 mg/m^2 intravenously, 1 mg/min every 3 weeks for 6 courses) (n = 184).

Main outcome measures
Overall and progression-free survival and clinical response.

Main results
Analysis was by intention to treat. At a median duration of follow-up of 37 months, the median overall survival and progression-free survival were longer in patients receiving paclitaxel and cisplatin compared with patients receiving cyclophosphamide and cisplatin (38 vs 24 mo, $P < 0.001$, and 18 vs 13 mo, $P < 0.001$, respectively). Clinical response was assessed in 216 women with clinically measurable disease. Treatment with paclitaxel and cisplatin led to more women having complete response than did treatment with cyclophosphamide and cisplatin (51% vs 31%, $P = 0.01$). {This absolute risk improvement of 20% means that 5 patients would need to receive 6 courses of treatment with paclitaxel and cisplatin (rather than cyclophosphamide and cisplatin) to achieve 1 additional complete response, 95% CI 3 to 15; the relative risk improvement was 64%, CI 18% to 130%.}* No difference existed between patients who received paclitaxel and those who received cyclophosphamide for pathologic complete response (assessed by laparotomy) (26% vs 20%), but fewer patients who received paclitaxel had macroscopic persistent disease (59% vs 76%, {$P < 0.001$}*).

Conclusion
Paclitaxel and cisplatin were more effective than cyclophosphamide and cisplatin in prolonging overall and progression-free survival and increasing clinical response rate in women with advanced ovarian cancer.

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*Numbers calculated from data in article.

Commentary

The initial management of patients diagnosed with epithelial ovarian cancer (90% of all ovarian cancer) is usually maximal debulking surgery followed by chemotherapy. Cisplatin or carboplatin, either alone or in combination with cyclophosphamide, are accepted as current standard treatments. Paclitaxel has been shown to be active in recurrent and refractory ovarian cancer. This important study by the GOG in the United States has now confirmed the efficacy of paclitaxel in the initial management of patients with ovarian cancer. The investigators have specifically chosen to include patients with bulky residual disease after surgery who have a poor outcome. The results are striking, with a substantial improvement in median overall survival (14 mo) and a smaller, although significant, improvement in relapse-free survival (5 mo). An important result of this study is that the proportion of patients with persistent disease at second-look laparotomy was lower in patients who received paclitaxel than in patients who received cyclophosphamide. In patients with minimal residual disease after surgery, therefore, the improvement in outcome may be even more substantial. This trial should be interpreted in the context of other trials being done in Europe, namely the International Collaborative Ovarian Neoplasm 3 trial, which compares carboplatin with carboplatin and paclitaxel, and the European Organization for Research and Treatment of Cancer trial (1). The results from these studies, in addition to those from smaller phase I and II trials that evaluate the dose and schedule of paclitaxel in combination, will be important for the future and valuable for establishing the role of this expensive drug in the initial management of patients with ovarian cancer.

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Reference

1. **Kaye SB, Piccart M, Aapro M, Kavanagh J.** Eur J Cancer. 1995;31A Suppl 4:S14-7.