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Carboplatin and Paclitaxel *versus* Cisplatin, Paclitaxel and Doxorubicin for first-line chemotherapy of Advanced Ovarian Cancer: A Hellenic Cooperative Oncology Group (HeCOG) study

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ABSTRACT

Introduction: The combination of Carboplatin and Paclitaxel is considered the standard of care as initial chemotherapy for Advanced Ovarian Cancer (AOC). We compared this regimen with the combination of Cisplatin, Paclitaxel and Doxorubicin.

Patients and methods: Patients with AOC were randomised to either six courses of Paclitaxel 175 mg/m^2 plus Carboplatin 7AUC or Paclitaxel at the same dose plus Cisplatin 75 mg/m^2 plus Doxorubicin 40 mg/m^2.

Results: Analysis was performed on 451 patients. The treatment groups were well balanced with regard to patient and disease characteristics. Performance status (PS) was better in the anthracycline arm. In terms of severe toxicity, the only significant difference between the two groups was the development of febrile neutropaenia in the anthracycline arm. Overall response rate was similar in both groups. With a median follow-up of 57.5 months, a marginal significance towards improved Progression-Free Survival (PFS) was noted in favour of the anthracycline arm, whilst there was no difference in overall survival. In multivariate

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analysis the hazard of disease progression at any time was significantly decreased by 25.5% for patients of the anthracycline arm.

Conclusion: The combination of Cisplatin, Paclitaxel and Doxorubicin demonstrates a marginal PFS improvement, but no additional survival benefit when compared with the standard Carboplatin/Paclitaxel regimen.

1. Introduction

The combination of platinum with a taxane is considered the standard of care for advanced epithelial ovarian cancer. Over the last decade, a number of well-designed studies have demonstrated its superiority over other regimens. In the GOG Protocol 111, Cisplatin at 75 mg/m^2 was combined with either Paclitaxel at 135 mg/m^2 as a 24-h infusion or Cyclophosphamide at 750 mg/m^2. The comparison favoured the Paclitaxel arm[1] in terms of clinical response, progression-free survival and median survival. With a follow-up of over 60 months, a 28% reduction in the risk of progression and a 34% reduction in risk of death were noted amongst those patients treated with Cisplatin/Paclitaxel as compared to Cisplatin/Cyclophosphamide.[2] Validation of these results became available from a large collaborative trial conducted in Europe and Canada. In this study, Paclitaxel was administered at 175 mg/m^2 over 3 h. The Paclitaxel – based arm was associated with improved response, progression – free survival and overall survival.[3] Other studies have indicated that the combination of Carboplatin and Paclitaxel is feasible and highly effective in ovarian cancer patients.[4] Three large randomised trials, which compared Cisplatin plus Paclitaxel *versus* Carboplatin plus Paclitaxel, did not show any differences in response rates, progression-free survival and overall survival between the two arms. Apart from demonstrating a better toxicity profile, the combination of Carboplatin with Paclitaxel had one more advantage: it made outpatient administration of chemotherapy feasible [5–7] for this group of patients. Therefore, the new combination became firmly established as the standard of care in first-line chemotherapy for advanced epithelial ovarian cancer. As expected it has extensively been used as the control arm for investigational trials over the past decade.[8]

The anthracyclines have demonstrated single-agent activity in platinum-pre-treated ovarian cancer[9] Two meta-analyses have shown a survival benefit for platinum/anthracycline-based combinations when compared with platinum-based combinations without anthracyclines.[10,11] A' Hern and Gore examined the impact of the addition of Doxorubicin to ovarian cancer regimens by performing an overview of data from meta-analyses. They concluded that the addition of Doxorubicin significantly improved survival.[12] These data have generated a significant interest in assessing the role of taxane/platinum/anthracycline combination in advanced epithelial cancer. Hill et al. reported preliminary results of a combination consisting of Cisplatin 75 mg/m^2, Paclitaxel 175 mg/m^2 over 3 h and Doxorubicin 50 mg/m^2 IV bolus every three weeks; G-CSF was used when neutrophils reached nadir. The regimen appeared active but also toxic.[13]

A similar study was reported by the GOG in which Paclitaxel 135 mg/m^2 IV over 24 h and Cisplatin 75 mg/m^2 were combined with escalating doses of Doxorubicin starting from 30 mg/m^2 with G-CSF support. Dose limiting toxicity was reached at the 40 mg/m^2 dose of Doxorubicin and included grade 4 neutropaenia (without neutropaenic fever) in all patients, renal toxicity and thrombocytopenia. Complete responses were observed in 89% of evaluable patients.[14]

Based on these data, we designed a prospective randomised trial to compare Carboplatin and Paclitaxel (standard arm) with Cisplatin, Paclitaxel and Doxorubicin plus G-CSF support (investigational arm) in the treatment of advanced epithelial ovarian cancer.

2. Objectives

The main objective was to evaluate overall survival (OS) and progression-free survival (PFS) and to compare possible differences between the two treatment arms. Secondary endpoints were to compare response rate and toxicity profile, which was expected to be of major importance for the Cisplatin, Paclitaxel and Doxorubicin arm.

3. Patients and methods

This was a prospective, multicentre, phase III study. Patients were enroled in 14 Oncology Centres in Greece.

To be eligible for the study, patients had to meet all the following inclusion criteria: (i) Histologically confirmed epithelial ovarian carcinoma FIGO stage IIc, III or IV. (ii) No previous chemotherapy, (iii) Laboratory values within normal levels (iv) Performance status (ECOG) $\leqslant$ 2, (v) No symptoms or signs of cardiac failure or acute coronary disease, (vi) Enrolment within six weeks from laparotomy, (vii) Patients' informed consent was necessary. There was no age restriction.

Patients with non-measurable or evaluable disease with either elevated or normal CA-125 levels at baseline were eligible for the study, but they were not evaluable for clinical response to chemotherapy.

Exclusion criteria included: (i) Other malignancy, except from non-melanoma skin cancer or radically excised *in situ* carcinoma of the cervix. (ii) History of atrial or ventricular arrhythmias and/or history of congestive heart failure; history of clinically and electrocardiographically documented myocardial infarction within the last 6 months or abnormal left ventricular ejection fraction (LVEF). (iii) Active infection or other serious medical conditions which would impair the ability of the patient to receive the treatment. (iv) Administra-