Comparison of Efficacies of Dose Dense Paclitaxel Plus Carboplatin and Conventional Paclitaxel Plus Carboplatin in the Treatment of Epithelial Ovarian Cancer

Veli SUNAR[1], Vakkas KORKMAZ[2], Koray ASLAN[3], Caner KOSE[4], Furkan SARICI[5], Zafer ARIK[6], Mehmet Mutlu MEYDANLI[7]

[1] Aydın Atatürk State Hospital, Medical Oncology Clinic, Aydın
[2] Ankara Etlik Zübeyde Hanım Training and Research Hospital, Gynecologic Oncology Clinic, Ankara
[3] Ankara City Hospital, Gynecologic Oncology Clinic, Ankara
[4] Ankara Etlik Zübeyde Hanım Training and Research Hospital, Obstetric and Gynecology Clinic, Ankara
[5] Medicana International Ankara Hospital, Medical Oncology Clinic, Ankara
[6] Hacettepe University Faculty of Medicine, Department of Medical Oncology, Ankara
[7] Gaziantep Medical Park Hospital, Gynecologic Oncology Clinic, Gaziantep, TURKEY

ABSTRACT

This study aims to compare efficacy of dose dense and conventionally dosed paclitaxel-carboplatin regimens in the first-line treatment of epithelial ovarian cancer (EOC). We evaluated the medical records of women with EOC followed in Zekai Tahir Burak Women's Health Training and Research Hospital between 2007-2019 retrospectively. The patients with Eastern Cooperative Oncology Group Performance Status of 0-1-2, and stages of IC-IV, without previous treatments, who had undergone primary cytoreductive surgery were included. All patients had received either dose dense paclitaxel-carboplatin (paclitaxel 80 mg/m^2 given on days 1, 8, and 15 plus carboplatin Area Under the Curve: 5 on day 1 of the 21 day cycle) or conventionally dosed paclitaxel-carboplatin (paclitaxel 175 mg/m^2 plus carboplatin Area Under the Curve: 5 on day 1 of the 21 day cycle) regimens in the first line treatment. Baseline clinicopathological features, progression-free survival, and overall survival were evaluated. This study included data of 133 patients. Forty patients had received dose dense regimen while 93 had conventionally dosed regimen. Median progression-free survival of the dose dense group [34.4 months (31.7 - 37.03)] was significantly longer than the conventional group [25.5 months (19.9-30.9)] [HR= 0. 55 (95% CI, 0.31 - 0.95), p= 0.03]. Median overall survival was 88.2 months (28.3 - 148.3) in the dose dense group and 76.5 months (63.3 - 89.7) in conventional group (p= 0.102).We have found improved progression-free survival in the first-line treatment of EOC with dose dense regimen compared to conventionally dosed regimen. Overall survival was longer in the dose dense group despite being not significant.

Keywords: Carboplatin, Chemotherapy, Ovarian epithelial carcinoma, Paclitaxel, Survival

INTRODUCTION

Ovarian cancer is the second most common gynecologic malignity and the leading cause of deaths due to gynecologic cancers.[1] Approximately 22,000 women are diagnosed with ovarian cancer in the United States annually and 14.000 women die from ovarian cancer.[2] The vast majority of patients have advanced disease at the time of diagnosis and develop recurrence within two years inspite of multimodal treatment combinations including cytoreductive surgery and chemotherapy.[3]

Platinum-taxan combination is the cornerstone of ovarian cancer treatment and has long been used as the standard regimen in the first-line therapy.[4,5] Several phase 3 studies revealed no survival advantage of adding a third cytotoxic agent to platinum-paclitaxel combination.[6-10] Demonstration of the fact that triple combination did not further improve outcomes, interest has aroused on the use of doublet chemotherapy in various schedules recently.

Dose dense therapy is a strategy which depends on decreasing the intervals between treatment cycles.

In this strategy, the drug is administered in shorter intervals keeping the cumulative dose constant. The rationale of dose dense therapy depends on the Norton-Simon's hypothesis which propounds that a shorter interval between cytotoxic treatment cycles would be more efficacious to decrease tumor burden than would dose escalation.[11]

Phase 3 trials demonstrated that weekly paclitaxel led to longer survival rates compared to 3-weekly paclitaxel in the treatment of breast cancer for both adjuvant setting and metastatic disease.[12,13] Similarly, it was shown that weekly paclitaxel was efficient and well-tolerated in the treatment of recurrent platinum-resistant ovarian cancer.[14-16] The first phase 3 study comparing weekly paclitaxel and paclitaxel every 3 weeks in the first-line treatment of ovarian cancer was reported from Japan and revealed higher progression-free survival (PFS) and overall survival (OS) in the weekly paclitaxel (dose dense) arm.[17,18] However, results of the following phase 3 studies were not in accordance with the Japanese Gynecologic Oncology Group (JGOG) study.[19-21] Considering results of all these phase 3 trials, the role of dose dense therapy is controversial in the current treatment algorithm. This study aimed to compare the efficacy of dose dense weekly paclitaxel-carboplatin versus conventionally dosed paclitaxel-carboplatin regimens in the first line treatment of epithelial ovarian cancer (EOC) retrospectively.

MATERIALS and METHODS

The medical records of patients with EOC who were followed in Zekai Tahir Burak Women's Health Training and Research Hospital between 2007-2019 were retrospectively analyzed. The baseline characteristics including age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), weight and height, baseline serum CA 125 levels, stage at diagnosis, histological subtype, history of surgery, first-line chemotherapy regimens, and number of cycles were analyzed. The study was approved by the local ethics committee with decision number of 37 and date of 25/02/2019.

The inclusion criteria were age >18 years, ECOG PS≤ 2 [22], no previous treatment, histopathologic diagnosis of EOC, execution of primary cytoreductive surgery, The International Federation of Gynecology and Obstetrics (FIGO) stage 1C-2-3-4 disease[23], and pre-treatment sufficient organ function (defined as not having liver or renal function impairment, and having sufficient bone marrow reserve). The exclusion criteria were neoadjuvant chemotherapy, ECOG PS > 2, non-epithelial ovarian carcinoma, other chemotherapy regimens than dose dense or conventionally dosed paclitaxel-carboplatin as first-line treatment, bevacizumab in combination with first-line chemotherapy, and maintenance therapy following the first-line treatment. All patients included had recieved either dose dense paclitaxel-carboplatin (dose dense therapy group: paclitaxel intravenous infusion at a dose of 80 mg per square meter of body-surface area on days 1, 8, and 15 of a 21-day cycle, plus carboplatin area under the curve [AUC]:5 intravenously on day 1 of the 21 day cycle) or conventionally dosed paclitaxel-carboplatin (conventional therapy group: paclitaxel intravenous infusion at a dose of 175 mg per square meter of body-surface area on day 1 of the 21 day cycle, plus carboplatin [AUC:5] intravenously on day 1 of the 21 day cycle) regimen as the first-line treatment. The Carboplatin dose was calculated using the Calvert formula.[24]

Baseline thorax and abdominal computed tomography (CT) were performed in all patients before starting treatment. Patients' liver and kidney function tests and complete blood count had been evaluated before every chemotherapy cycle. Disease status was evaluated after the 3rd and 6th cycles during chemotherapy. After completion of chemotherapy, patients were followed once every three months in first 2 years, then every six months for the following 3 years, and annually thereafter for the follow-up monitoring. Every follow-up session comprised physical examination, serum CA125 levels, chest X-rays, and abdominal ultrasound. CT was not performed routinely in every visit except for patients whose CA125 levels increased, who had symptoms suggesting progressive disease or ones with signs of progressive disease in basal imaging.[25]

Progressive disease was defined according to the RECIST version 1.1 depending on the radiological and clinical indicators of disease progression.[26] Asymptomatic isolated increase in CA 125 levels

was not considered as progressive disease. These patients were followed every three months with clinical evaluation and radiologic imaging until progressive disease according to the RECIST criteria was detected. Optimal cytoreduction corresponds to residual disease ≤ 1 cm in maximum tumor diameter whereas suboptimal cytoreduction is defined as residual disease > 1 cm after resection.[27-29] The PFS was calculated as the period of time from primary cytoreductive surgery date to detection of progressive disease or death (whichever occurs first). The OS was defined as the period of time from diagnosis date to death (whatever the death cause is). For the patients who were alive at date of analysis, the last visit date was accepted as the death date for analyses. The baseline clinicopathological characteristics of patients at diagnosis, PFS, and OS were assessed retrospectively.

Statistical Analysis

All statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) for Windows v.21.0 (SPSS, Inc. Chicago, IL). Parametric data were defined as mean ± standard deviation (SD) and, non-parametric data were presented as median and range. Categorical variables were given with numbers and percentages and compared by means of chi square test. For comparisons of numerical data between groups, independent-t test was used for parametric data and Mann Whitney U test was used for the non-parametric data. Survival rates were determined by Kaplan-Meier method. Comparison of chemotherapy regimens was performed by log-rank test. Cox proportional hazards model was employed to determine hazard ratio (HR) and 95% confidence intervals (CI). $p< 0.05$ was accepted as statistically significant.

RESULTS

The study included 133 patients with a mean age of 53.3± 9.4 years. The mean body mass index (BMI) was 28.6 ± 5.8 kg/m^2. The median serum CA 125 was 263.5 (7-18152) mg/dl and median number of chemotherapy cycles was 6 (3-8). Of the patients, 83.3 % had median ECOG PS of I, 65.4% had high-grade serous carcinoma (HGSC) histology and 65.4% were stage III.

Table 1. Baseline clinicopathological characteristics of study cohort

Age (years), mean±SD	53.3±9.4
BMI (kg/m^2), mean±SD	28.6 ± 5.8
ECOG PS, number (%)	
0	18 (13.5)
I	111 (83.5)
II	4 (3)
CA 125, median (range)	263.5 (7-18152)
Histological type, number (%)	
HGSC	87 (65.4)
LGSC	10 (7.5)
Endometrioid carcinoma	16 (12)
Clear cell carcinoma	10 (7.5)
Mixed epithelial carcinoma	7 (5.3)
Carcinosarcoma	3 (2.3)
Stage, number (%)	
I	22 (16.5)
II	16 (12)
III	87 (65.4)
IV	8 (6)
Type of surgery, number (%)	
Suboptimal	13 (9.8)
Optimal	120 (90.2)
Chemotherapy regimen, number (%)	
Dose dense regimen	40 (30.1)
Conventional regimen	93 (69.9)
Chemotherapy cycles, median (range)	6 (3-8)
Recurrence, number (%)	
Yes	73 (54.9)
No	60 (45.1)
Death from disease, number (%)	
Yes	39 (29.3)
No	94 (70.7)

BMI: Body mass index, SD: standart deviation, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HGSC: High-grade serous carcinoma, LGSC: Low-grade serous carcinoma

Of the patients, 90.2% had undergone optimal primary cytoreductive surgery while 9.8% had suboptimal surgery. Thirty percent of the patients had received dose dense regimen (n= 40) while 69.9% had conventionally dosed regimen (n= 93). The median follow up time was 35.9 months (5.3-135.7). By the data analysis date (September, 2020), 73 patients (54.9%) had recurrent disease and 39 patients (29.3%) had died. The clinicopathologic characteristics of the study cohort were presented in Table 1.

Table 2. Comparison of conventional group and dose dense group

	Conventional group (n= 93)	Dose Dense group (n= 40)	p
Age (years), mean±SD	54.9±9.9	49.5±6.8	0.002
BMI (kg/m^2), mean±SD	29.4 ± 6.8	27.8±4.4	0.217
ECOG PS, number (%)			0.302
0	11 (11.8)	7 (17.5)	
I	78 (83.9)	33 (82.5)	
II	4 (4.3)	0 (0)	
CA 125, median (range)	218.5 (7-18152)	408.5 (7-5000)	0.091
Histological type, number (%)			
HGSC	59 (63.5)	28 (70)	0.372
LGSC	7 (7.5)	3 (7.5)	
Endometrioid carcinoma	13 (14)	3 (7.5)	
Clear cell carcinoma	8 (8.6)	2 (5)	
Mixed epithelial carcinoma	3 (3.2)	4 (10)	
Carcinosarcoma	3 (3.2)	0 (0)	
Stage, number (%)			
I-II	28 (30.1)	10 (25)	0.550
III-IV	65 (69.9)	30 (75)	
Type of surgery			
Suboptimal	9 (9.7)	4 (10)	0.515
Optimal	84 (91.3)	36 (90)	
Chemotherapy cycles, median (range)	6 (3-8)	6 (3-8)	0.640
Recurrence, number (%)			
Yes	57 (61.3)	16 (40)	0.024
No	36 (38.7)	24 (60)	
Death from disease, number (%)			
Yes	36 (38.7)	3 (7.5)	< 0.001
No	57 (61.3)	37 (92.5)	

BMI: Body mass index, SD: standart deviation, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HGSC: High-grade serous carcinoma, LGSC: Low-grade serous carcinoma

Comparisons

The study cohort was divided into two groups as conventional group (n= 93) and dose dense group (n= 40) based on their chemotherapy regimens. The groups were similar in terms of BMI, ECOG PS, serum CA 125 level, FIGO stage, type of surgery, and median number of chemotherapy cycles (p> 0.05). The mean age of the patients in the dose dense group was significantly lower than the patients in the conventional group. [49.5 ± 6.8 years vs 54.9 ± 9.9; p= 0.002].

By the data cut of date (September, 2020), 36 patients (38.7%) of the conventional group and 3 patients (7.5%) of the dose dense group had died (p< 0.001). While recurrence was detected in 57 patients (61.3%) in the conventional group, 16 patients (40%) had recurrence in dose dense group during follow-up (p= 0.024). The median follow up time was significantly longer in the conventional group [43.9 months (5.3-135.7) vs 32.2 months (10.9-102.5) respectively, p= 0.035]. Table 2 summarizes the comparison of two groups.

Survival Analysis

Median OS was 88.2 months (28.3 - 148.3) in the dose dense group and 76.5 months (63.3 - 89.7) in conventional group. The difference was not statistically significant (p= 0.102, Figure 1). Median PFS of the dose dense group [34.4 months (31.7-

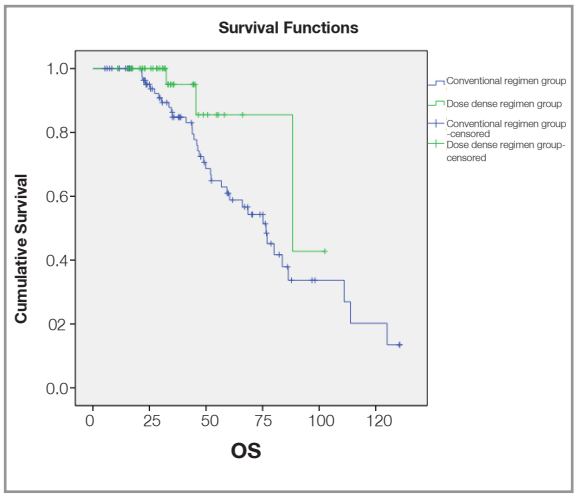

Figure 1. The comparison of Overall Survival rates between dose dense and conventional groups

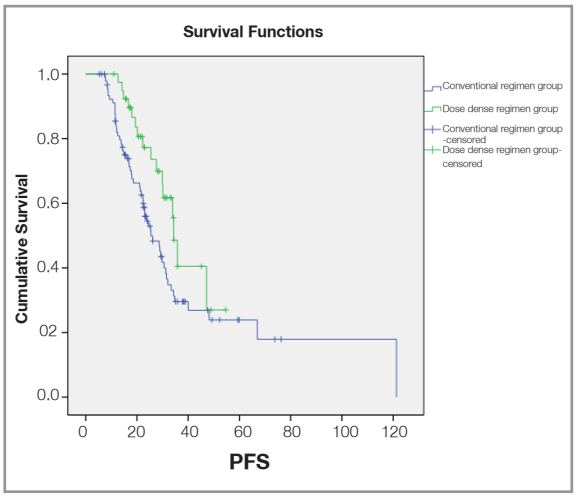

Figure 2. The comparison of Progression-free Survival rates between dose dense and conventional groups

37.03)] was significantly longer than the conventional group [25.5 months (19.9-30.9)] [HR= 0. 55 (95% CI, 0.31 - 0.95), p= 0.03, Figure 2].

When only patients who had undergone optimal cytoreduction were assessed, PFS was 47.1 months (31.5 - 62.8) in the dose dense group and 28.9 months (22.3 - 35-5) in conventional group yielding a statistically significant difference [HR= 0. 50 (95 % CI, 0.26-0.95), p= 0.033]. Although OS was longer in the dose dense group compared to conventional group in patients having undergone optimal cytoreductive surgery, the difference did not reach statistical significance [88.2 months vs 76.5 months, p= 0.095].

DISCUSSION

This retrospective study compares the efficacy of dose dense and conventionally dosed paclitaxel-carboplatin regimens in the first-line treatment of EOC. We analyzed a total of 133 patients who had undergone either optimal or suboptimal primary cytoreductive surgery with varying stages of 1C-4. We found significantly longer PFS in patients receiving dose dense regimen compared to the conventional regimen group. OS was also longer in the dose dense group whereas the difference was not significant.

Platinum-paclitaxel combination administered every 3 weeks has been used for more than 2 decades and constitutes the standard first-line treatment of EOC.[3-5] The studies investigating the role of dose dense regimen in the treatment of EOC present inconsistent outcomes and no consensus is available on this issue. The first phase 3 study comparing dose dense paclitaxel-carboplatin and conventionally dosed paclitaxel-carboplatin regimens in the treatment of EOC was reported by the JGOG in 2009. This study remarked better OS and PFS in the dose dense group.[17] Long term survival analysis revealed an OS benefit of 38 months (100 months vs 62 months) in favor of dose dense regimen.[18] This survival advantage is striking and rare in EOC. That study revealed a novel treatment option for the first-line treatment of EOC. Unlike the JGOG 3016 study, phase 3 ICON8 trial did not detect PFS difference between dose dense and conventional regimen groups.[21] Additionally, that study compared the conventionally dosed paclitaxel-carboplatin with weekly paclitaxel-carboplatin regimen and reported no PFS difference. Despite being well designed randomized controlled phase 3 trials, these two studies exhibit inconsistent results. While primarily European patients were included in the ICON8 study, the JGOG 3016 study enrolled Asian patients. Some authors consider that these conflicting results may be due to pharmacogenomic differences between ethnic origins. In this study where we present our real life experience, we can depict that our results are similar to the JGOG study that enrolled the Asian participants.

Approximately half of the patients recruited in the JGOG trial had suboptimal cytoreduction. This study reported that patients undergoing suboptimal cytoreduction benefited more from the dose dense treatment. Moreover, the subgroup analysis suggested that dose dense regimen did not improve outcomes in patients with mucinous and clear cell carcinoma histology. In our study cohort, 10% had undergone suboptimal surgery. Therefore, we did not perform further analyses due to low patient number in the suboptimal surgery group. However, considering that 90% of both study groups had optimal surgery, we can postulate that dose dense regimen improves outcomes in patients with optimal cytoreduction. This study cohort comprises 8 patients with clear cell histology in the conventional group and 2 patients in the dose dense group. No patients with mucinous histology were included. It is not easy to put forward an idea on how dose dense treatment affects the outcomes due to low number of these histologic subtypes.

The GOG 262 study investigated how addition of bevacizumab to either dose dense or conventionally dosed chemotherapy affect outcomes in the first line treatment of EOC.[20] Of the participants, 84% used bevacizumab along with chemotherapy. While there was no PFS difference between arms among patients using bevacizumab in combination to chemotherapy, there was significantly longer PFS in the dose dense group among patients receiving chemotherapy only.[20] This study indicates the importance of dose dense regimen in countries where bevacizumab is not approved for the first-line treatment of EOC or where it is not available. Likewise, the national health insurance of our country does not approve the first-line bevacizumab use, thus our cohort does not contain patients using bevacizumab.

The most prominent limitation of our study is not presenting adverse effect data due to the retrospective design. Since we could not reach all patients' safety data from medical records, we could not report toxicity data systematically. Another limitation is lower median age of patients in the dose dense group. This may be a consequence of the retrospective design. All patients' treatment choices were performed according to the patients and physicians' preferences impeding a bias in patient selection. Histopathological features and other demographic characteristics except for age were well balanced across groups. The strong element of our study is presenting our real life data in the first-line treatment of EOC on which a clear consensus is lacking and even phase 3 trials report inconsistent results. Moreover, this is the first report from Turkey regarding this issue.

As a consequence, this study found improved PFS in patients receiving dose dense paclitaxel-carboplatin regimen than conventionally dosed therapy in the first-line treatment of EOC. Whilst OS was longer in the dose dense arm, the difference did not reach statistical significance.

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Correspondence:

Dr. Veli SUNAR

Aydin Ataturk Devlet Hastanesi

Medikal Onkoloji Bölümü

Kurtulus Mahallesi, Cumhuriyet Caddesi No= 61

Efeler, AYDIN / TURKEY

Tel: (+90-555) 560 80 24

e-mail: velisunar@gmail.com

ORCIDs:

Veli Sunar	0000-0003-4672-4621
Vakkas Korkmaz	0000-0002-0953-6210
Koray Aslan	0000-0002-3432-7381
Caner Kose	0000-0002-3044-4804
Furkan Sarici	0000-0001-9662-3760
Zafer Arik	0000-0002-0598-389X
Mehmet Mutlu Meydanli	0000-0001-6763-9720