Histopathological Efficacy of Docetaxel Versus Paclitaxel As First Line Chemotherapy for Epithelial Ovarian Carcinoma✍

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OBJECTIVE: To evaluate and compare efficacy of docetaxel and paclitaxel combining with carboplatin in the first line chemotherapy of epithelial ovarian carcinoma according to hystopathological findings of second look laparatomy.

STUDY DESIGN: Thirty two patients having stage II-IV epithelial ovarian cancer (17 cases in the paclitaxel-carboplatin group,15 cases in the docetaxel-carboplatin group) and operated in Department of Obstetrics and Gynecology, Division of Gynecologic Oncology were entered in this study. The cases were randomized for the treatment. All cases had inform-consent about the treatment options and second look procedures. The cases who completed chemotherapy and had a second look laparatomy were included the study. Pathological responses were evaluated with second look findings proved with biopsy. Statistical analyses were performed with Chi square and Mann-Whitney U tests. Survival analyses were calculated with using Kaplan-Meier survival analyses and Log Rank test. P>0.05 was accepted for statistical significance.

RESULTS: There were no differences in demographic characteristics and rate of optimal cytoreduction between two groups. Eight cases (47,1%) in the paclitaxel-carboplatin group and 3 cases (20%) in the docetaxel-carboplatin group were hystopathological tumor positive in the second look operation without statistically significance. Also there was no significant difference between two groups in mean survival time(p 0.06).

CONCLUSION: Efficacy of docetaxel and paclitaxel are the same in terms of hystopathological findings of second look laparatomy in the treatmet of first-line epithelial ovarian cancer.

Key Words: Paclitaxel, Docetaxel, Ovarian cancer

Gynecol Obstet Reprod Med;14:3 (189 - 192)

Introduction

Ovarian cancer is the most lethal gynecological malignancy despite of improving survival with aggressive cytoreduction and comprehensive chemotheraphy.[1] Because 60% of the patients are diagnosed in advanced stages and there is no screening method to diagnose ovarian cancer in early stages. Sometimes to detect early stages, patients should be lucky with having symptoms or going to physician for routine gynecological evaluations.

Many chemotherapeutic agents have activity in ovarian cancer as a single or in combinations. But two chemotherapeutic agents groups including platinum and taxanes are the most active drugs. Platinum group is the cornerstone of almost all chemotherapy protocols in ovarian cancer. Platinum combined with taxanes are now seen to be more suitable protocol to treat advanced stages of ovarian cancer. Two mainstay drugs in taxane group are paclitaxel and docetaxel. The role of paclitaxel in the treatment of ovarian cancer is well established,[2,3] but the other member of this family, docetaxel, has been developed and used less frequently. Docetaxel has similarities with paclitaxel as an active agent in ovarian carcinoma but differs from paclitaxel in respect to toxicities. In the experimental studies on ovarian carcinoma, it is more potent agent than paclitaxel.[4,5] In the clinical trials, docetaxel is detected as a equal active agent with paclitaxel.[6] In all of these studies, response rate is evaluated with clinically. There is no data in the literature according to med-line (pub med) addressing to response rate is evaluated and compared according to histopathological results of second look procedures. So mainly, we compared docetaxel with paclitaxel prospectively in respect to pathological evaluation during second look procedure.

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Submitted for Publication: 06.07.2008
Accepted for Publication: 28.09.2008

✍*: This study was presented as a poster presentation in the 15th ESGO International Meeting held in Berlin, Germany, October 28-November 1, 2007*

Material and Method

Initially, totally 40 patients diagnosed and operated between 2004 and 2005 in the Department of Obstetrics and Gynecology Division of Gynecological Oncology, were entered in the study. But 5 (25%) patients in docetaxel and 3 (15%) patients in paclitaxel group without second look laparatomy because of clinical incomplete response were excluded from the study. The patients had cytoreduction by the same team and it was approved optimally when largest residual tumor was less than 1-2 cm. All the patients had an inform consent and randomized consequently into each group. The patients who had chemotherapy prior to surgery were excluded. Paclitaxel 175 mgr/m^2 for 3 hour infusion and docetaxel 75 mgr/m^2 for over 1 hour infusion were administered. Carboplatin was given as 5 AUC for two groups. Dexametason and granisetron were given at the same schedule before and after chemotherapy courses in two groups. Chemotherapy courses were repeated in every 3 weeks if there was no contraindication. Dose reduction was performed in patients with grade 4 hematological toxicities. The patients were followed for toxicity with full blood count(hemoglobin, white blood cell, red blood cell, platelet etc), biochemical profile [liver tests (SGOT, SGPT), renal functional tests (BUN, Creatinin, creatinin clearance) and glucose level etc.] after 10 day and before every chemotherapy course. For the neurological toxicity, the patients were evaluated clinically. If the patients had symptoms or findings showing to neurological toxicity, they were evaluated by neurologist performing EMG. Toxicity were grouped according to GOG toxicity criteria. Physical and gynecological examination were made before in every chemotherapy course. CA125 plasma level was measured before in every course. Pelvic and upper-abdominal CT scan and Chest x-ray were performed after 3rd and 6th courses of chemotherapy. After 6 courses of chemotherapy, the patients having clinical complete response (no symptoms related to disease, normal physical and gynecological examination, normal blood tests defined above and no measurable disease in CT-scan and Chest x-ray) were submitted to second look laparatomy. Also for the second look laparatomy, all the patients informed and if the patient agreed it was performed. In the second look laparatomy, abdominal cytology were taken and multiple biopsy (vaginal cuff, infundibulopelvic ligaman, random peritoneal, biopsy from adhesion and suspicious lesions, rest of omentum) were performed. Statistical analyses were performed with Chi-square test, Mann-Whitney U test, Kaplan-Meier survival analysis and Log rank (Mantel-Cox) test using SPSS 13 statistical program. P< 0,05 was accepted for statistical significance.

Results

Mean age was 53,2 (33-72) and mean gravida 4,2 (1-8) for all patients. Totally 32 patients having second look procedures were grouped as 17 paclitaxel and 15 docetaxel group, respectively. There was no difference in demographic characteristics between two groups (Table 1). Also no difference was observed in the rate of optimal cytoreduction and hystologic types (Table 1). According to second look histopathological findings, in the paclitaxel group, 8 cases (47,1%) had histopathologic positive tumor compared 3 (20%) cases in the docetaxel group, respectively. But this difference was not statistically significant (p 0,1). This rate may depend on the sample size. Grade 3 and 4 toxicities were not different (Table 1). There were no significant difference in follow-up time, mean and median survival time between two groups (Table 2 and Figure 1).

Table 1. Characteristics of the patients.

Characteristic	Paclitaxel group, n (%)	Docetaxel group, n(%)	P
Mean age	54,9(37-70)	50,6(33-72)	NS
Mean gravida	4,7(1-8)	4,1(1-5)	NS
Histologic type			
Serous	11(64,7)	9(60,0)	NS*
Endometrioid	3(17,6)	3(20,0)	NS
Musinous	1(5,9)	1(6,7)	NS
Clear cell	-----	1(6,7)	
Mixed	2(11,8)	1(6.7)	NS
Stage II	2(11,8)	2(13,3)	
III-IV	15(88,2)	13(86,7)	NS
Optimal cytoreduction			
Yes	15(88,2)	12(80)	NS
No	2(11,8)	3(20)	
Pathological response			
Complete	9(52,9)	12(80,0)	NS
Incomplete	8(47,1)	3(20,0)	
Anemia (grade 3 and 4)	2(11,8)	1(6,7)	NS
Leucopenia (grade 3 and 4)	1(5,9)	2(13,3)	NS
Trombocytopenia (grade 3 and 4)	2(11,8)	1(6,7)	NS
Neutropenic fever	1(5,9)	1(6,7)	NS

**: Not Significant*

Table 2. Follow-up and survival analysis

Type	Follow-up(Months)			Survival(Months)		
	Mean(SD*)	Median	P	Mean(SE**)	Median(SE)	P
Docetaxel	27,1(8,6)	29	NS	31,5(1,0)	32(1,1)	NS
Paclitaxel	28,0(6,0)	31		32,6(0,8)	34(0,9)	

SD: Standard Deviation, SE: Standard Error

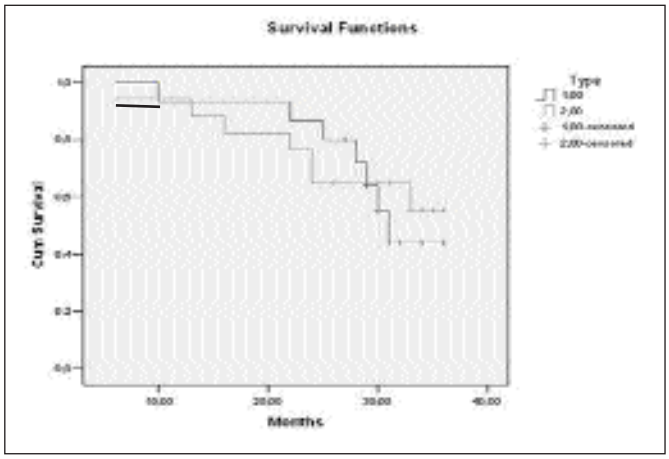

Figure 1. Cumulative survival curves of two types(Type1: Docetaxel, Type 2: Paclitaxel)(P 0,7. Log Rank Test).

Discussion

Ovarian carcinoma is the leading cause of death in women with gynecologic malignancy.

The most important factor affecting prognosis is optimal cytoreduction which is approved as the largest residual tumor diameter less than 1 cm. Rate of optimal cytoreduction depends on many factors including tumor characteristics and biology, patient performance, hospital situation and surgeon. If the surgeon is specialized in gynecologic oncology, rate of maximal cytoreduction increases.[7] In our study it is very high. In the literature, rate of optimal cytoreduction is in very wide range (up to 85%).[8] Surgeon should do maximal effort for reducing tumor volume to zero without increasing patients morbidity and mortality.

Comprehensive chemotherapy is the second most important factor for the treatment of ovarian cancer. There are many chemotherapeutic agents which are active in ovarian cancer as a single or in combination form. There are two important group of agents which are used in combination form widely. Platinum group including cis-platinum or carboplatinum which are the most used drugs are the corner-stone of all combinations. Carboplatinum is preferable drug having the same efficacy with cis-platinum but less serious toxic adverse effects.[9]

The second important agents for treating ovarian carcinoma is taxane group. Paclitaxel and docetaxel are the most familiar drugs in taxane group. Paclitaxel is the first taxane approved and used in the chemotherapy of ovarian carcinoma. Its activity in ovarian carcinoma in combination with platinum is reported in many studies.[2,3,10,11] Also paclitaxel improves survival when compared to cyclophosphamide[12] and it is used widely now.

Docetaxel is a semisanthetic taxane which is popular in Europe. Docetaxel inhibits microtubuli formation as paclitaxel.[13] But in preclinical studies, it is more potent agent than paclitaxel in ovarian carcinoma.[4,5] However, in clinical trial and in this study, it is found that two drugs have the same activity.

Beside of treatment success, toxicities of drugs are very important. However, paclitaxel and docetaxel are two members of the same family, they are having different toxicity profiles. Actually, it is not known how they make these different effects. Paclitaxel is more toxic for neurological system, but docetaxel for hematological system, respectively. Also two drugs are toxic for the gastrointestinal system and skin.[14]

Response to chemotherapy can be evaluated by clinical or pathological. Clinical response is evaluated with examination of patients, CA125 level and radiological tests including CT-scan, sonography and PA-chest x-ray. If all these methods does not detect any findings refer to tumor, it is accept as clinical complete response. At that time, second look procedures may be suggested to patients. Also, it is well known, in clinical complete response, about 40% of the patients have microscopic disease during second look procedures. On the other hand, because of invasivities and without proved clinical benefit of second look procedures, they are investigational methods, not routine part of management. In this trial it was approved by the patients. In fact that, second look procedures predict prognosis of patients well. So in the study, patients responses were mainly evaluated with histo-pathological examination doing biopsy during second look laparatomy. Residual tumor was more common in paclitaxel group without statistical significance. This insignificant difference may arise from sample size or different action of the drugs. This result should be investigated in studies having large sample size.

Second look procedures can be performed with laparatomy and laparascopy. Due to examination whole abdominal cavity and touching organs, laparatomy is over than laparascopy. But less hospital stay, pain and no longer incision are advantages of laparascopy. We preferred laparatomy as a conventional method for evaluating patients.

Conclusion

Docetaxel and paclitaxel have the same efficacy to treat advanced stages (II-IV) of ovarian cancer according to second look surgical findings.

Epitelyal Over Kanserlerinin Birincil Kemoterapisinde Paklitaksel'e Karşılık Dosetaksel'in Histopatolojik Etkinliği

Epitelyal over karsinomlarının ilk basamak kemoterapisinde karboplatin ile birlikte paklitaksel ve dosetakselin etkinliğinin ikincil bakış laparatomisinin histopatolojik bulgularına göre

değerlendirilmesi ve karşılaştırılması.

Evre II-IV epitelyal over kanserli (17 vaka paklitaksel-karboplatin, 15 vaka dosetaksel-karboplatin grubunda) ve Kadın Hastalıkları ve Doğum Departmanı Jinekolojik Onkoloji Ünitesinde opere edilen 32 hasta çalışmaya alındı. Vakalar tedaviler için randomize edildi. Tüm vakalardan tedaviler ve ikincil bakış laparatomisi için bilgilendirilmiş onam alındı. Kemoterapisini tamamlayan ve ikincil bakış laparatomisi yapılan hastalar çalışmaya dahil edildi. Patolojik cevap biyopsi ile kanıtlanmış ikincil bakış laparatomi bulguları ile değerlendirildi. İstatistiksel analizler X2 ve Mann-Whitney U testleri ile yapıldı. Survival analizleri Kaplan-Meier yaşam analizi ve log Rank testi kullanılarak yapıldı. P ≤0,05 istatistiksel anlamlı kabul edildi.

İki grup arasında demografik özellikler ve optimal sitoredüksiyon oranları bakımından fark yoktu(p ≥0,05). Sekiz kişi paklitaksel, 3 kişi dosetaksel grubunda ikincil bakış laparatominin histopatoloji bulgularına göre istatistiksel anlamlı olmayarak tümor saptandı. Keza ortalama yaşam süresi iki grup arasında farksızdı (p 0,06).

İkincil bakış laparatomisinin histopatolojik bulgularına göre dosetaksel ve paklitaksel epitelyal over kanserlerinin birincil tedavisinde benzer etkilidir.

Anahtar Kelimeler: Paklitaksel, Dosetaksel, Over kanseri

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