Survival Analysis of Ovarian Carcinosarcomas Depending on Platinum or Doxorubicin Based Adjuvant Chemotherapy

İlker SELÇUK[1], İpek DÜZGÜNER[2], Sevda BAŞ[1], Taner TURAN[2], Afra ALKAN[3], Nurettin BORAN[2], Mehmet Mutlu MEYDANLI[1], Gökhan TULUNAY[2]

Ankara, Turkey

ABSTRACT

OBJECTIVE: To analyse the survival outcomes of women with ovarian carcinosarcoma according to platinum or doxorubicin based adjuvant chemotherapy protocols.

STUDY DESIGN: This retrospective study was performed at Etlik Zübeyde Hanım and Zekai Tahir Burak Women's Health Education and Research Hospitals, which are tertiary centers in Turkey. A total of 31 women with ovarian carcinosarcoma between January 1999 and January 2013 were evaluated retrospectively.

RESULTS: The mean age of patients was 53.84±10.13. Most of the patients were diagnosed with stage IIIC ovarian carcinosarcoma (n=21, 67.7%). Maximal debulking and optimal debulking was performed to 23 (74.2%) and 8 (25.8%) patients, respectively. Disease free survival was significantly shorter in stage IIIC patients when compared to stage IIIB patients (p=0.048). Disease free survival for one and three years according to the treatment protocol (platinum or doxorubicin based) was not significantly different (p=0.574). Additionally, three and five years overall survival was not significantly different (p=0.891) between the platinum and doxorubicin based chemotherapy protocols.

DISCUSSION: We did not find a significant difference in terms of disease free survival and overall survival between platinum and doxorubicin based adjuvant chemotherapy protocols in women with ovarian carcinosarcoma.

Keywords: Ovarian carcinosarcoma, Chemotheraphy, Survival, Platinum, Doxorubicin

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Introduction

Ovarian carcinosarcomas (OCSs) are very rare histologic subtypes of ovarian cancer and they account for approximately 1% of ovarian carcinomas.[1] They are also termed as malignant mixed mullerian tumors (MMMTs). Carcinosarcomas contain both mesenchymal and epithelial elements. Epithelial elements may consist of serous, endometrioid, clear cell or undifferantiated adenocarcinomas. The mesenchymal components could be homologous or heterologous according to the tissue type whether seen at the ovarian locus or not. The tumorigenesis of OCS is controversial and three main theories shape the literature: 1) the collision theory suggests two independent tumor types, epithelial and sarcoma that they collide 2) the combination theory suggests a single stem cell precursor forming both carcinoma and sarcoma 3) the conversion theory suggests that the sarcomatous elements arise from the carcinoma during tumor evolution.[2] OCSs are generally seen in nulliparous, postmenopausal women and they are aggressive tumors with a poor prognosis and survival.[3] There is not a consensus regarding the optimal treatment schedule for OCSs and the prospective data are lacking. Debulking surgery followed by adjuvant chemotherapy had shown improved outcomes.[4] However, the ideal adjuvant chemotherapy for OCSs is unclear.[2] Limited studies and retrospective analyses shape the literature. We evaluated the effect of adjuvant chemotherapy (Platinum or Doxorubicin based) on survival periods in women with OCS.

Material and Method

Institutional Ethical Board approved this retrospective study was performed at Etlik Zübeyde Hanim and Zekai Tahir Burak Women's Health, Education and Research Hospitals. A

[1] *Gynecologic Oncology Unit Zekai Tahir Burak Women's Health, Education and Research Hospital, Ankara*

[2] *Gynecologic Oncology Unit, Etlik Zubeyde Hanım Women Diseases, Education and Research Hospital, Ankara*

[3] *Department of Biostatistics, Yıldırım Beyazit University Faculty of Medicine, Ankara*

Address of Correspondence: *İlker Selçuk*
Gynecologic Oncology Unit Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey
ilkerselcukmd@hotmail.com

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total of 31 women with OCS between January 1999 and January 2013 were evaluated retrospectively and patients' data were retrieved from the computerized database of gynaecological oncology clinics. All the operations were performed by the same senior gynaecological oncologists and pathological specimens were reviewed by the pathologists specialized on gynaecological oncology.

Variables consisting of age at diagnosis, parity, menopausal status, presenting symptom, preoperative serum Ca125 level, quantity of ascites detected during surgery, tumor diameter, debulking level, adjuvant chemotherapy, disease free survival (DFS) and overall survival (OS) were evaluated. All patients were staged based on International Federation of Gynecology and Obstetrics (FIGO) staging criteria for ovarian cancer, 2010. The routine surgical procedure was total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy and pelvic-paraaortic lymph node dissection. Disease free survival was stated as the time between the end of first line chemotheraphy and the date of recurrence. Overall survival was stated as the time between the date of diagnosis and the death of patient or the last time that the patient was seen. Debulking level was categorized as maximal or optimal. Maximal debulking was defined as no residual tumor after initial surgery. Optimal debulking was defined as <1cm residual tumor after the initial cytoreductive surgery.

Adjuvant chemotherapy was mainly based on platinum or doxorubicin. Paclitaxel/Carboplatin protocol was performed with 175 mg/m^2 paclitaxel and carboplatin with an AUC (Area Under Curve) of 5 every 21 days for 6 cycles. Cyclophosphamide/Doxorubicin/Cisplatin protocol was performed with cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2 and cisplatin 50 mg/m^2 every 3 weeks for 6 cycles. Doxorubicin/Carboplatin protocol was performed with doxorubicin 50 mg/m^2 and carboplatin with an AUC of 5 every 3 weeks for 6 cycles. Ifosfamide/Mesna/Doxorubicin protocol was performed with ifosfamide 2.5 g/m^2, mesna 2.5 g/m^2 and doxorubicin 60 mg/m^2 every 21 days for 6 cycles.

Statistical analyses were performed with SPSS for Windows version 17.0 statistical package (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean±SD, discrete variables as median (range), and categorical variables as number (percentage). Kaplan-Meier test, Cox regression model and log-rank test were performed for the analysis of survival data. A p value <0.05 was considered to be significant.

Results

There were 31 cases of OCS identified between 1999 and 2013. The mean age and parity of patients were 53.84±10.13 (ranging between 40-77 years) and 3.69±2.6 respectively. Three patients (9.6%) were nulliparous. Twenty-four patients (77.4%) were postmenopausal. Abdomino-pelvic pain (n=11, 35.4%) and abdominal distension (n=10, 32.2%) were the leading symptoms of patients. Patients generally admitted with a tumor mass of 100-149mm (n=12, 38.7%). Twenty-eight women (90.3%) had elevated preoperative serum Ca125 levels. Twenty-one women (67.7%) had ascites during the initial operation. Maximal debulking and optimal debulking were performed to 23 (74.2%) and 8 (25.8%) patients respectively. Most of the patients were diagnosed with stage IIIC OCS (n=21, 67.7%). Five patients (16.1%) were with stage IIIB disease. Table 1 shows the clinicopathologic features of patients.

Table 1: Patient characteristics with clinicopathological features

Characteristics	n (%)
Patients	31
Median age	62
Range	40-77 years
Postmenopausal	24 (77.4%)
Elevated Ca-125	28 (90.3%)
Ascites presentation	21 (67.7%)
Mean tumor diameter	13.7±5.1 cm
Stage	
IC	1 (3.2%)
IIIB	5 (16.1)
IIIC	21 (67.7%)
IV	4 (12.9%)
Debulking	
Maximal	23 (74.2%)
Optimal	8 (25.8%)

We performed adjuvant chemotherapy to 30 patients (one patient did not come to follow-up visits and treatment was scheduled at an outer hospital so she was excluded from the survival analysis). Twenty-three patients (76.6%) received platinum based chemotherapy and 6 patients (20%) received doxorubicin based chemotherapy (Table 2). Seventeen of 23 women (74%) treated by platinum based chemotherapy and 5 of 6 women (83.3%) treated by doxorubicin based chemotherapy had maximal debulking surgery. One patient received imatinib as an adjuvant therapy. Disease free survival (DFS) was significantly shorter in patients with stage IIIC disease when compared to stage IIIB disease (p=0.048). However there was not any difference between stage IV and stage IIIC diseases in terms of DFS. Median DFS and OS for patients receiving platinum based chemotherapy were 29 and 50 months, respectively. On the other hand, median DFS and OS for women receiving doxorubicin based chemotherapy were 17 and 37 months, respectively. DFS for one and three years according to the treatment protocol (platinum or doxorubicin based chemotherapy) was not significantly different between the groups (p=0.574) (Figure 1). Additionally, three and five years OS was not significantly different between the platinum and doxorubicin based chemotherapy protocols (p=0.891) (Figure 2). One patient who received only imatinib as adjuvant therapy had a DFS of 28 months (m) which is noteworthy and promising.

Table 2: Adjuvant chemotheraphy protocols

Chemotheraphy protocol	n (%)
Platinum based	23 (76.6%)
Paclitaxel/Carboplatin	23 (100%)
Doxorubicin based	6 (20%)
Cyclophosphamide/Doxorubicin/Cisplatin	1 (16.6%)
Ifosfamide/Mesna/Doxorubicin	4 (66.6%)
Doxorubicin/Carboplatin	1 (16.6%)
Imatinib	1 (3.3%)

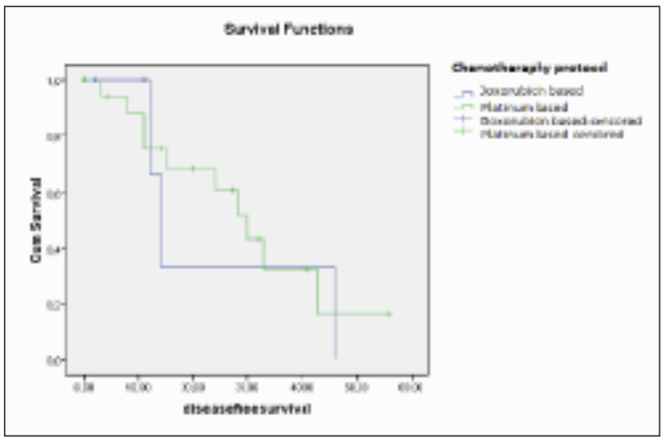

Figure 1: The relationship between disease free survival and chemotherapy protocols

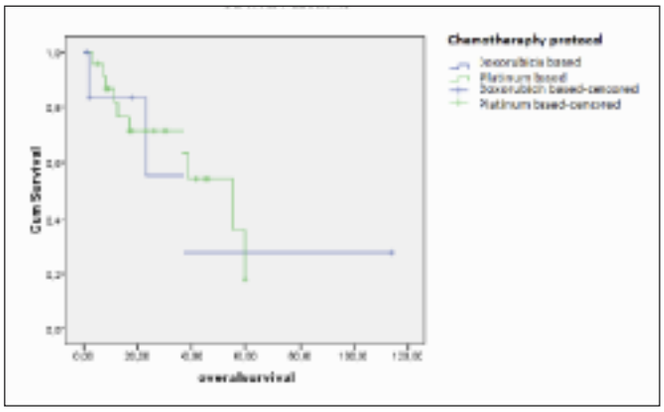

Figure 2: The relationship between overall survival and chemotherapy protocols

Discussion

OCS is a very rare and aggressive form of ovarian carcinoma. The pathogenesis of OCS is under debate. Although three theories cover the literature, histogenetic analysis favor a common epithelial stem cell to form a carcinosarcoma.[5] Previously the predominant stromal tissue was proposed as the major prognostic factor.[6] However, in a recent analysis it was offered that this tissue component does not change the prognosis.[7]

OCSs have similar properties with epithelial ovarian cancer (EOC). Sixth decade is the median age range of diagnosis and these patients commonly admit with the symptoms of abdominal distention, pain and discomfort. Additionally these patients mostly present with FIGO stage III-IV disease and have the symptoms of an advanced disease with elevated Ca125 levels.[8-10] We found similar results in the current study that the median age of patients was 62 years and abdomino-pelvic pain was the most common symptom. In our study, most patients were with stage IIIC disease (67.7%) and ascites with elevated Ca125 levels were common findings associated with these tumors. Most of the patients whether in early or advanced stage disease had elevated preoperative serum Ca125 levels.

In women with OCS, primary extensive cytoreductive surgery with adjuvant chemotherapy showed improved outcomes in the retrospective data.[4] Optimal cytoreduction leads to increased disease free and overall survival rates when compared to surgery with a residual disease.[1,11,12] We performed maximal and optimal debulking to 23 (74.2%) and 8 (25.8%) patients respectively. Cytoreductive surgery has been reported as a significant prognostic factor for patients with stage III-IV disease.[12]

Surgery with adjuvant chemotheraphy shapes the basic treatment schedule of OCS. On the other hand, a standard chemotherapy protocol for OCS is still under debate. Platinum based chemotherapy had been largely studied in the literature with favourable outcomes in contrast to the poor prognostic nature of disease. Mok et al.[13] reported good results with platinum based chemotherapy; the median survival time was 46m and overall survival rate for 1, 2 and 5 years was 60%, 40% and 20% respectively. Thus platinum agents could be used at the initial protocol with effective results. Leiser et al.[14] also described platinum as first line treatment option for OCS. They found complete and partial response rates as 40% and 23%, respectively. Additionally, the median time to progression was 12 m with a 30% progression rate. The median OS was 43 m with 53% and 30% survival rates for 3 and 5 years, respectively. Loizzi et al.[10] also applied adjuvant platinum based chemotherapy and found OS as 17 m. Chang et al.[15] reviewed 37 ovarian carcinosarcoma patients and they found histologic type as an insecure marker of survival. Additionally, they found overall median survival approximately 9 months, with 40% and 6% survival rates for 1 and 5 years follow-up respectively.[15] Sood et al.[4] evaluated 41 patients, they found patients receiving platinum based chemotherapy had a higher response rate and median survival. Duska et al.[16] found complete clinical response rate 55% when platinum was used as first line therapy. They offered platinum based therapy as an effective method.

Jernigan et al.[17] compared platinum and non-platinum based chemotherapy for OCSs. They did not detect a survival benefit with platinum. In 1986 Morrow et al.[18] analysed doxorubicin as first line treatment agent and they did not find a clinically active response. Nevertheless the role of doxoru-

bicin for OCS is insufficient with approximately 10% response rates.[19] Gomez-Raposo et al.[20] applied pegylated liposomal doxorubicin to one patient as a second-line theraphy and they stated a complete response with acceptable toxicity. Although there are controversies regarding the first line treatment; platinum based chemotherapy seems as the most efficacious method in several studies. We did not find a significant difference in terms of survival between platinum and doxorubicin based chemotherapy protocols. The limited number of patients especially on the doxorubicin arm represents the main weakness of this study. However, OCS is a very rare disease. For this reason, we think that our experience and findings are worthy to be reported.

One patient in our study received imatinib as an adjuvant protocol. We detected a disease free survival of 28 m for this patient. Despite the usage of imatinib in uterine carcinosarcomas with a promising profile,[21] more studies are needed in order to support the clinical use of imatinib as an adjuvant in OCSs. The promising results with targeted therapies might give rise to the investigation profile of imatinib in OCS.

Conclusion

Although OCSs are rare and highly mortal malignancies with an aggressive behaviour; maximal cytoreductive surgery seems to increase the survival rates. Although there is a tendency towards platinum based chemotherapy in the literature, our results suggest that doxorubicin based chemotherapy can be an option for selected patients.

Overyan Karsinosarkom Hastalarının Platin veya Doksorubisin Bazlı Adjuvan Kemoterapi Protokolüne Bağlı Olarak Sağ Kalım Analizi

ÖZET

AMAÇ: Overyan karsinosarkomlu hastaların platin veya doksorubisin bazlı adjuvan kemoterapi protokolüne bağlı olarak sağ kalım analizini yapmak.

GEREÇ VE YÖNTEM: Bu retrospektif çalışma Türkiye'de tersiyer merkezler olan Etlik Zübeyde Hanım ve Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastaneleri'nde yapılmıştır. Ocak 1999 ve Ocak 2013 tarihler arasında tanı alan 31 olgu incelenmiştir.

BULGULAR: Hastaların ortalama yaşı 53,84±10,13' dir. Çoğu hasta Evre IIIC over karsinosarkomu ile tanı almıştır (%67,7). Yirmiüç (%74,2) hastaya maksimal tümör indirgeme cerrahisi, 8 (%25,8) hastaya ise optimal tümör indirgeme cerrahisi yapılmıştır. Evre IIIC hastalarda hastalıksız sağ kalım Evre IIIB hastalara göre kısa bulunmuştur (p=0,048). Bir ve üç yıllık hastalıksız sağ kalımlar platin veya doksorubisin kemoterapisi alan hastalar arasında farklı olarak bulunmamıştır (p=0,574). Aynı zamanda üç ve beş yıllk kaba sağ kalım süreleri de platin veya doksorubisin kemoterapileri alan hasta grupları arasında farklı değildir (p=0,891).

SONUÇ: Overyan karsinosarkomlu hastalarda platin veya doksorubisin bazlı adjuvan kemoterapi protokolü arasında hastalıksız sağ kalım ve kaba sağ kalım açısından anlamlı bir farklılık yoktur.

Anahtar Kelimeler: Overyan karsinosarkom, Kemoterapi, Sağ kalım, Platin, Doksorubisin

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