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ORIGINAL ARTICLE

Adjuvant platinum-based chemotherapy in patients with epithelial ovarian cancer: prognostic factors and final outcome

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Summary

Purpose: *Epithelial ovarian cancer (OVCA) prognosis depends on the clinical stage, histological grade and surgical cytoreduction. Our goal was to retrospectively analyze several prognostic factors in relation with the final outcome in patients with OVCA subjected to adjuvant platinum (PL)-based chemotherapy (CT).*

Methods: *Three hundred OVCA patients were treated at the Department of Medical Oncology A΄, "Metaxa" Cancer Hospital, between 11/1989-3/2010. Of those, analyzed were patients with R0 debulking operation, treated with adjuvant PL-based CT. Their clinico/imaging/pathological findings and serum tumor marker CA 125 levels were analyzed and related to relapse rate (RR), progression-free survival (PFS) and overall survival (OS).*

Results: *Out of 53 R0 OVCA patients 35 (66%) experienced long-term PFS (median follow up time 63 months, range 5-195^{+}) and 18 (34%) relapsed after a median of 19 months. Fifteen of the 18 relapsing patients were treated with first-line CT. Twelve (80%) of them were PL-sensitive and 3 (20%) PL-resistant. Their median PFS was 9 and 3 months in PL-sensitive and PL-resistant cases, respectively (p=0.073). Statistical analysis of prognostic factors demonstrated FIGO stage and abnormal postoperative CA 125 values as significant. Patients with FIGO stage III had significantly shorter PFS (p=0.002) and OS (p=0.078) than those in earlier stages, and patients with abnormal postoperative CA 125 values had significantly worse PFS (p=0.017) but not OS (p=0.386) than those with normal values. Age, histological subtype and grade did not affect PFS and OS.*

Conclusion: *FIGO stage and abnormal postoperative CA 125 have prognostic significance in OVCA patients after R0 surgical therapy and adjuvant PL-based CT. Patients with PL-sensitive disease achieved better results during therapy for relapse.*

Key words: ovarian cancer, adjuvant chemotherapy, optimal surgical debulking, prognostic factors

Introduction

OVCA is the second most common gynecologic malignancy and is the most common cause of death among women with gynecologic cancers [1]. In most women the disease is diagnosed at a clinical stage where primary cytoreductive surgery, followed by chemotherapy is considered the standard of care [2-5]. Cumulative knowledge from prospective and retrospective studies suggests that OVCA prognosis depends on the clinical stage at the time of diagnosis (defined by the International Federation of Gynecological Oncology - FIGO), the histological grade and subtype, and the extent of surgical debulking. FIGO stages (I-II vs. IIIa-IIIc) at the time of diagnosis, together with the surgical disease debulking (optimal vs. suboptimal) clearly remain the primary factors defining the prognosis of these patients [6-10]. Consequently, women with advanced OVCA and suboptimal surgical debulking with residual tumor volume >1 cm will have poor prognosis, even after receiving PL-based chemotherapy (combined with paclitaxel), the gold standard to date. On the other hand, patients with early-stage disease with optimal cytoreductive surgery (R0) defined

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as no macroscopically disease left behind, will be able to receive the same CT combination regimen but in an adjuvant setting this time and will experience the best long term survival [6,7,10-14]. Taking all these into consideration, we assessed the 3 decades' experience of our Department in the treatment of the gynecological cancer, and retrospectively analyzed several prognostic factors in relation with the final outcome in patients with OVCA subjected to R0 debulking operation followed by adjuvant PL-based CT.

Methods

Patients

Out of 300 patients with OVCA treated at the Department of Medical Oncology A΄ of "Metaxa" Cancer Hospital, Greece, from 11/1989 till 3/2010, selected for analysis were those with R0 debulking operation. All of them had received standard adjuvant PL-based CT. All surgical procedures were performed by qualified surgeons. All patients were routinely staged preoperatively and postoperatively with physical examination, chest x-ray, abdominal CT scan, bone scan, full blood count, serum biochemistry and CA 125 marker levels estimation. Additional requirements included a World Health Organisation (WHO) performance status (PS) of 0-2 and absence of serious disabling diseases that would prevent primary cytoreductive surgery or PL-based CT.

Study design

Data were collected from patient medical records of the Department of Medical Oncology A΄, "Metaxa" Cancer Hospital. The study protocol was approved by the Hospital Ethics Committee. Patients with optimal surgical debulking (R0) were analyzed. All of them had received adjuvant PL-based combination regimens. Their clinico/imaging/pathological findings including patient age, histological subtype, grade, pre and postoperative CA 125 serum levels and stage were analyzed for RR, PFS and OS. Progression of disease after adjuvant chemotherapy was defined according to RECIST criteria. PL-sensitive patients were defined those whose relapse was > 6 months after the adjuvant CT completion. Accordingly, PL-resistant were characterized patients whose relapse was confirmed < 6 month period after adjuvant chemotherapy. Tumor response during chemotherapy after relapse was evaluated according to WHO criteria [15,16]. All patients, including those who suffered from disease progression were followed up and the outcome of the first-line CT they received was also analyzed.

Follow up

Patients were followed 3-monthly after completion of adjuvant CT by means of clinical examination, full blood count, serum biochemistry, CA 125 serum tumor marker estimation, chest x-rays and abdominal CT scan.

Statistical analysis

Analysis was conducted using the Statistical Package for Social Science (SPSS, version 14.0) software. Univariate and multivariate analysis were performed according to Cox regression method. Cox models estimated univariate and multivariate hazard ratios for each candidate predictor of interest: age, stage, grade, histological subtype, CA 125, etc. Only variables that had prognostic significance in the univariate analysis where included in the multivariate model. OS, PFS, RR were calculated according to the Kaplan-Meier method. All tests were two-sided. A level of $p<0.05$ was considered statistically significant.

Results

Out of 300 OVCA patients 53 (17.6%) were rendered R0 with debulking operation. Their median age was 52 years (range 18-82). All patients had received 6 cycles of adjuvant PL-based CT, starting about one month after surgical staging and debulking. Twenty patients received cisplatin/paclitaxel, 12 carboplatin/paclitaxel, 12 carboplatin/cyclophosphamide, 1 cisplatin/cyclophosphamide and 8 patients cisplatin combined with other drug, according to the gold standard of the different time periods and patients' special needs (Table 1). Among 53 patients, 35 (66%) experienced long-term PFS during for a median follow up period of 63 months (range 5-195^{+}) and 18 (34%) relapsed after a median of 19 months (range 1-66, Figure 1). Relapse

Table 1. Adjuvant chemotherapy regimens administered after optimal debulking

Postoperative chemotherapy regimens	*Number of patients (%)*
Cisplatin/paclitaxel	20 (37)
Carboplatin/paclitaxel	12 (23)
Cisplatin/cyclophosphamide	1 (2)
Carboplatin/cyclophosphamide	12 (23)
Cisplatin/other	8 (15)

was determined using CT scan and CA 125 serum marker, accompanied by biopsy when necessary and possible. Fifteen of the 18 relapsing patients (83%) were treated with first-line chemotherapy. The remaining 3 presented with very advanced disease, poor PS and comorbidities making them unsuitable for chemotherapy. Twelve patients (80%) were PL-sensitive, and 3 (20%) were characterized as PL-resistant. Among retreated patients, 5 (33%) achieved again complete remission (CR) (two of them were long-term CRs), 2 (13%) achieved partial response (PR), 2 (13%) stable disease (SD) and 6 (40%) progressive disease (PD). In the PL-sensitive group there were 5 CRs, 1 PR, 2 SD and 4 PD, whereas in PL-resistant there were 1 PR and 2 PD. PFS was 9 months (range 2-22) and 3 months (range 2-8) in PL-sensitive and PL-resistant cases, respectively (p=0.073; Figure 2). PL-sensitive patients received PL-based CT and PL-resistant received paclitaxel and gemcitabine/pegylated doxorubicin as second line CT.

Patients were also analyzed according to FIGO stage (Table 2), histological subtype (Table 3), tumor grade (Table 4) and postoperative CA 125. Thirty-seven patients were FIGO stage I and II and 16 FIGO stage III. Twenty-three patients had serous, 14 endometrioid, 11 clear cell and 5 mucinous OVCA. Thirty patients had grade I and II OVCA and 23 grade III. Median postoperative CA 125 value was 16 U/ml (range 1.9-382), while 18 (34%) patients had abnormal values (>35 U/ml).

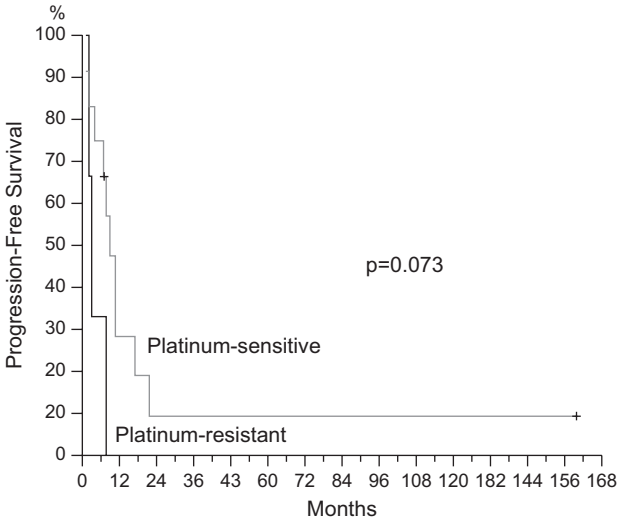

Figure 2. Progression-free survival of patients treated with second-line chemotherapy according to platinum sensitivity.

Statistical analysis demonstrated FIGO stage and postoperative CA 125 values as significant for patients' survival. Patients with FIGO stage III had shorter PFS (p=0.002) (Figure 3) and OS (p=0.078) than those with lower stages, and patients with abnormal postoperative CA 125 values had significantly worse PFS (p=0.017) (Figure 4) but not OS (p=0.386) than those with normal CA 125 values. The effect of age, histological subtype

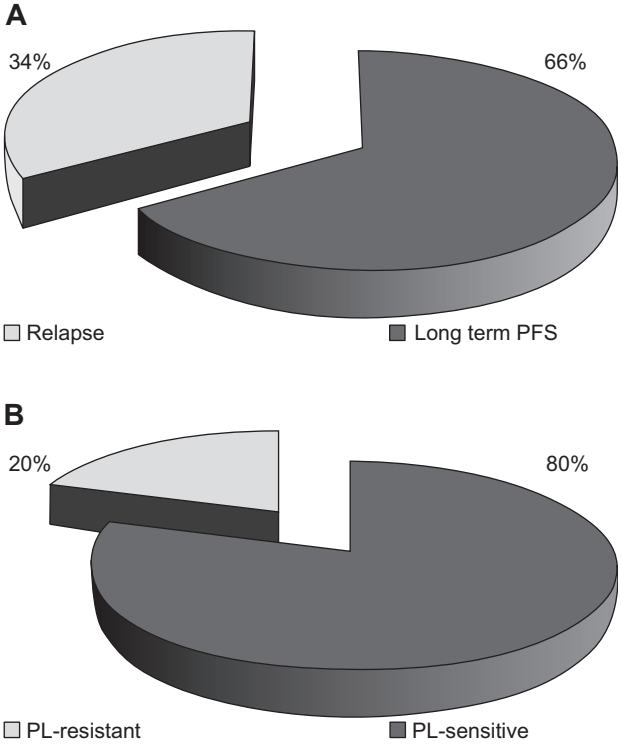

Figure 1. A: Patients with long-term progression-free survival (PFS) and relapse. **B:** Platinum sensitivity.

Table 2. Number of patients according to FIGO stage

FIGO stage	*Number of patients (%)*
I	25 (47)
II	12 (23)
III	16 (30)

Table 3. Number of patients according to histological subtype

Histological subtype	*Number of patients (%)*
Serous	23 (43)
Endometrioid	14 (27)
Clear cell	11 (21)
Mucinous	5 (9)

Table 4. Number of patients according to grade

Grade	*Number of patients (%)*
I	4 (8)
II	26 (49)
III	23 (43)

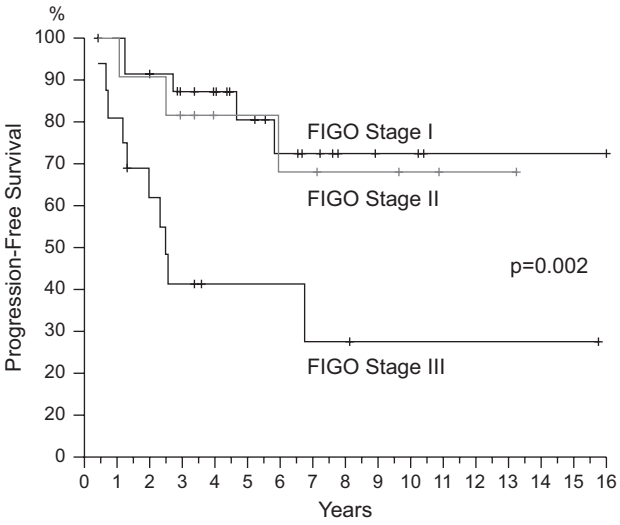

Figure 3. Progression-free survival of patients treated with first-line chemotherapy according to FIGO stage.

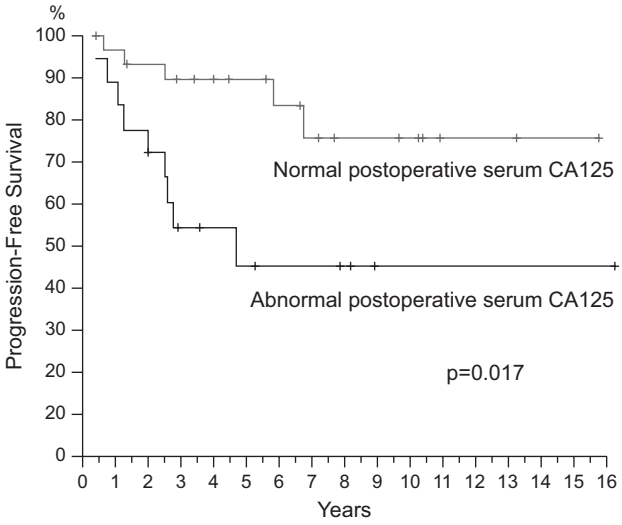

Figure 4. Progression-free survival of patients treated with first-line chemotherapy according to postoperative serum CA 125 values.

and grade of differentiation on PFS and OS was not statistically significant (Tables 5,6).

Discussion

OVCA accounts for the 90% of all malignant tumors of the ovary and is the leading cause of gynecologic cancer deaths. Approximately 25% of women present with FIGO stage I, 15% with stage II, 42% with stage III and 17% with stage IV [1]. A large amount of data demonstrate that survival is better for women who start postoperative CT in the presence of low disease burden, supporting the need for optimal cytoreduction in these patients [5,17-22]. As a result, FIGO stage emerges as the most important prognostic factor. Other important prognostic factors include patient's age and PS. Histological subtype and grade do not seem to affect prognosis, however mucinous, clear-cell and high grade carcinomas behave more aggressively [23]. The role of postoperative PL-based CT is established and the combination of carboplatin plus paclitaxel is the standard of care regimen [18-20].

We tried to retrospectively analyze the final out-

Table 5. Prognostic factors for progression-free survival

Univariate analysis	*Hazard ratio*	*95% Confidence interval*	*p-value*
Abnormal vs. normal CA125	3.816	1.271-11.452	0.017
Grade (3 vs. 1-2)	1.373	0.544-3.469	0.502
FIGO stage (III vs. I-II)	4.328	1.690-11.083	0.002
Histology (clear cell, mucinous vs. endometrioid, serous)	0.542	0.178-1.649	0.281
Age (above vs. below median)	2.056	0.796-5.310	0.136
Multivariate analysis	*Hazard ratio*	*95% Confidence interval*	*p-value*
Abnormal vs. normal CA125	3.119	1.014-9.595	0.047
FIGO stage (III vs. I-II)	2.955	1.006-8.675	0.049

Table 6. Prognostic factors for overall survival

Univariate analysis	*Hazard ratio*	*95% Confidence interval*	*p-value*
Abnormal vs. normal CA125	2.897	0.262-32.042	0.036
Grade (3 vs. 1-2)	1.153	0.186-7.141	0.878
FIGO stage (III vs. I-II)	5.060	0.832-30.782	0.078
Histology (clear cell, mucinous vs. endometrioid, serous)	1.626	0.268-9.842	0.597
Age (above vs. below median)	5.241	0.584-46.993	0.139

come of patients with OVCA after optimal cytoreductive surgery followed by PL-based CT in relation with FIGO stage, CA 125 serum tumor marker, histological subtype and grade of differentiation. According to our results, FIGO stage emerged as the most critical prognostic factor for PFS and OS. Postoperative CA 125 was found statistically significant with regard to PFS but not to OS. Histological subtype, age, and grade did not affect prognosis in our patient group.

In the second-line setting, PL-sensitive patients seem to achieve better results including long-term CR. Patients with longer PFS tend to respond better in retreatment. The PL-resistant patients had poor outcomes, as expected.

In conclusion, our data suggest that FIGO stage and PL-sensitivity are the most crucial prognostic factors in patients with OVCA after optimal R0 cytoreductive surgery and adjuvant PL-based CT.

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