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Research Article

The Clinical Characteristics and Treatment Results

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Abstract

Background: It is well known that clear cell carcinoma of the ovary (CCC) demonstrates different clinical behaviors from other epithelial ovarian cancer and has strong association with endometriosis, thromboembolic complication, hypercalcemia, and large pelvic mass. The introduction of cisplatin-based chemotherapy significantly changed the postoperative management of ovarian cancer patients. Different studies showed a better response rate of CCC to chemotherapy with paclitaxel plus carboplatin regime than with the conventional platinum-based regimens.

Aim: The purpose of this study was to evaluate the patients' clinical characteristics and treatment results for clear cell carcinoma (CCC) of the ovary treated in paclitaxel-platinum chemotherapy in comparison with those treated in conventional platinum-based chemotherapy after primary surgery

Methods: We retrospectively reviewed the medical records of 40 patients with CCC who received treatment in the department of obstetrics and gynecology, Samsung Medical Center from March, 1996 to April 2006. The clinical characteristics, treatment results and follow-up data were collected from medical records and/or telephone surveys.

Results: Mean age was 47 years (range 30–72 years). Patients with age less than 50years were 62.5%. Tumors were 15% (6/40) stage IA, 2.5% (1/40) stage IB, 37.5% (15/40) stage IC, 5% (2/40) stage II, 32.5% (13/40) stage III, and 7.5% (3/40) stage IV. Patients with CCC were more likely to have FIGO stage I & II disease than FIGO stage III & IV (60% vs. 40%). Five-year progression-free survival and overall survival were 91% and 80% in stage I & II, 36% and 55% in stage III & IV, respectively (5-yr PFS; P<0.01, 5-yr OS; P=0.03). With a median follow-up of 45 months (2-112 months), 75% (18/24) of stage I/II patients are alive, while 19% (3/16) of stage III/IV patients are alive. 37.5% (15/40) of the patients presented with endometriosis. Except for one patient who was referred by a local clinic, all patients underwent cytoreductive surgery. The rate of optimal debulking (≤ 1cm residual tumor diameter) was 90% (36/40). Overall, for women treated with platinum-based chemotherapy, 75% (27/36) had clinically complete responses to adjuvant chemotherapy. But there was no survival benefit according to chemotherapeutic differences in the patients who received cytoreductive surgery followed between conventional platinum-based chemotherapy (CAP or CP) and by paclitaxel and platinum-based chemotherapy (P=0.40). Univariate analysis showed that stage was the only favorable prognostic factor for women with clear cell carcinoma of the ovary (P=0.04).

Conclusions: Our results suggest that CCC has a distinct clinical behavior, similar to previous studies, that frequently presents at early- stages and is associated with endometriosis. In addition, there was a close correlation between the level of CA-125 and survival, and there was no survival benefit according to chemotherapeutic differences. ［CAP (CP) VS TP(TC)］

Key Words: clear cell carcinoma; ovary; platinum-based chemotherapy

Introduction

Clear cell carcinoma has been recognized as a distinct histological entity in the World Health Organization classification of ovarian tumors since 1973. The precise incidence of this tumor is unknown but estimated to be 5–10% of all epithelial ovarian cancers diagnosed [1]. Clear cell carcinoma of the ovary (CCC) is a distinctive subtype of epithelial ovarian cancer that demonstrates different clinical behaviors from other epithelial ovarian cancer [2-5]. Several studies have reported that CCC has a high incidence rate of endometriosis, thromboembolic complication, hypercalcemia, and large pelvic mass. CCC tends to present at earlier stages, with 59~71% of all patients presenting with stage I and II disease. Although half of the patients have stage I disease at the diagnosis, they have poorer prognoses than do those with other epithelial ovarian cancer [2, 6-8]. A significant proportion of women (20–50%) with stage I clear cell ovarian carcinoma have recurrences and die of their malignancies[2].

The introduction of cisplatin-based chemotherapy in the late 1970s

markedly changed the postoperative management of ovarian cancer patients. Nonetheless, the results and value of these newer efforts and therapies applied to clear cell carcinoma are yet undetermined [2, 9, 10]. The most distinctive characteristic is that CCC has a low response rate to chemotherapy [7, 11-15]. The response rate of chemotherapy for CCC was 11.1% with platinum-based regimens [11] and 22-56% with paclitaxel 64 plus carboplatin [16]. In the study by Goff et al, overall, 70% of the 23 evaluable patients with stage III OCCA showed progression of disease while on platinum-based chemotherapy, which is significantly different from the 29% rate of progressive disease observed in patients with papillary serous carcinoma [9].

We conducted the retrospective study to evaluate the clinical characteristics of the patients with CCC of the ovary and to compare treatment results of paclitaxel-platinum chemotherapy with those treated in conventional platinum-based chemotherapy after primary surgery.

Materials and Methods

We retrospectively reviewed the medical records of 40 patients with CCC who received treatment in obstetrics and gynecology department, Samsung Medical Center from March 1996 to April 2006. Data were collected from medical records and telephone surveys. All pathological specimens (3outside specimens) from primary surgery were reviewed by pathologists worked at Samsung Medical Center. Two of the 40 patients had mixed – type (papillary, sarcomatous type) CCC.

34patients underwent surgical staging including total hysterectomy, bilateral salpingooophorectomy, omentectomy, intraperitoneal cytology, with/without pelvic and/or para-aortic lymphadenectomy. The other 6 patients underwent total hysterectomy, bilateral salpingooophorectomy. Thirty-eight of the 40 patients with CCC (95%) received platinum-based chemotherapy after the initial surgery. among 38patients who received chemotherapy, one of 2 patients received only one cycle of TP and the other received one cycle of TC, and then they did not receive any more chemotherapy. So, they were excluded from the evaluation of the response to chemotherapy. 30 patients received adjuvant chemotherapy combining paclitaxel 135mg/m2 and cisplatin 75mg/m2 (20cases), or paclitaxel 175mg/m2 and carboplatin (AUC=5) (10cases) at every 3 weeks . 6 patients received combination therapy of cyclophosphamide 500mg/m2, Adriamycin 50mg/m2 and cisplatin 50mg/m2 (CAP) (1case) or cisplatin 50mg/m2 and cyclophosphamide 750mg/m2 (CP)(5cases) at every 3 weeks.

Response to chemotherapy was evaluated with CT or MRI for patients with clinically measurable disease, according to RECIST criteria or assessed in patients with non-measurable disease, according to the level of CA-125 combined with CT/MRI. By definition of RECIST criteria, a complete response (CR) was defined as the complete disappearance of all detectable disease for at least 4 weeks. A partial response (PR) was defined as a $\geq$ 30% decrease in tumor size for at least 4 weeks. Stable disease (SD) was defined as the absence of any significant change in measurable lesions for at least 4 weeks. Progressive disease (PD) was defined as the appearance of a new lesion or a $\geq$20% increase in tumor size. According to the level of CA125, PD was defined as the elevation of CA125 to $\geq$2 x UNL or $\geq$2 x nadir value.

The time to progression was defined as the interval from the date of primary surgery until the date of documented recurrence or tumor progression (PD). The Survival duration was determined as the time from the date of primary surgery until death or the date of last follow-up contact.

Statistical Methods

Patient survival distribution was calculated using the Kaplan–Meier method. The significance of the survival distribution in each group was tested by the log rank test. The hazard ratios with 95% confidence intervals (95%CIs) were estimated by using a Cox's proportional hazard model to evaluate prognostic factors for survival. A P- value of 0.05 was considered statistically significant.

Result

The characteristics of Patients are summarized in Table 1.

Characteristics	No of patients (%)
All case	40
Age(years)	
Mean age	47(30~72)
<50	25(62.5)
≥50	15(37.5)
FIGO Stage	
I	22(55)
IA	6(15)
IB	1(2.5)
IC	15(37.5)
II	2(5.0)
IIA	0(0)
IIB	0(0)
IIC	2(5)
III	13(32.5)
IIIA	0(0)
IIIB	4(7.5)
IIIC	9(22.5)
IV	3(7.5)
Presence of endometriosis	
Yes	15(37.5)
No	25(62.5)
Preoperative CA-125 level	
Mean(range) <100 U/ml >100 U/ml	793(4.8~14640) 22(55) 18(45)
Residual tumor diameter	
<1cm	36(90)
>1cm	4(10)
Postoperative chemotherapy	
CAP(CP)	6(15)
Paclitaxel + cisplatin(carboplatin)	32(80)
None	2(5)

Table.1. *the characteristics of patients with clear cell carcinoma of the ovary*

The median age of the 40 patients was 47 years (range 30~72years). The Median duration

Of follow–up was 45months (range 4~112months). Patients with age less than 50years were 62.5% and those more than 50years were 37.5%. According to the classification of the International Federation of Obstetrics and Gynecology (FIGO), Tumors were 15% (6/40) stage Ia, 2.5% (1/40) stage Ib, 37.5% (15/40) stage Ic, 5% (2/40) stage II, 32.5% (13/40) stage III, and 7.5% (3/40) stage IV, respectively. Of the 40 patients with CCC, the level of Preoperative CA-125 was more than 100 U/ml in 18patients (45%), less than <100U/ml in 22patients (55%). 37.5% (15/40) of the patients with CCC presented with endometriosis. The rate of optimal debulking (≤ 1cm residual tumor diameter) was 90% (36/40**).** (Table1).38patients (95%) with CCC received platinum-based chemotherapy after initial surgery. among 38patients who received chemotherapy, one of 2patients received only one cycle of TP and the other received one cycle of TC. They did not any more chemotherapy. One of two patients died of disease (DOD), the other did not receive follow-up. So, those 2patients were therefore excluded from the analysis for response of adjuvant chemotherapy. Among 2patients without receiving chemotherapy, one has been NED status; the other developed recurrence and died of renal failure. 30patients received adjuvant chemotherapy combining paclitaxel 135mg/m2 and cisplatin75mg/m2 (20cases), or paclitaxel 175mg/m2 and carboplatin (AUC=5) (10cases) at every 3weeks. 6patients received combination therapy of cyclophosphamide 500mg/m2, adriamycin 50mg/m2 and cisplatin 50mg/m2 (CAP) (1case) or cisplatin 50mg/m2 and cyclophophamide 750mg/m2 (CP)(5cases) at every 3 weeks. For women treated with platinum-based chemotherapy, the overall clinical response rate was 89%, including a CR in 75% (27/36) and a PR in 14% (5/36), to adjuvant chemotherapy. SD was 8% (3/36) and PD was 3% (1/36) (**Table2**). Current status of patients at last f/u was NED in 20(50%) cases, AWD

		CAP(CP)	Paclitaxel+ cisplatin(carboplatin)	Chemo(-)	Total (%)

Response	CR	6(100)	21(70)		27(75)
	PR	0	5(17)		5(14)
	SD	0	3(10)		3(8)
	PD	0	1(3)		1(3)
	Total	6	30		36
Current status at last F/U	NED	4(67)	15(50)	1(25)	20(50)
	AWD	0	5(17)	0	5(13)
	DOD	2(33)	10(33)	2(50)	14(35)
	F/U loss			1(25)	1(2)
	Total	6	30	4	40

Table 2. *Response of adjuvant-chemotherapy and current status at last F/U*

But there was no survival benefit according to chemotherapeutic differences in the patients who received cytoreductive surgery followed by conventional platinum-based chemotherapy (CAP or CP) or paclitaxel and platinum-based chemotherapy (P=0.82 & P=0.40). (Table3).

		Hazard ratio			
Variables	No	Univariate (95%CI)	p- value	Multivariate (95%CI)	p-value
Age			0.63		0.93
≤50	27	1		1	
>50	13	1.31(0.43-4.02)		0.93(0.20-4.32)	
Parity			0.11		0.22
Nulliparous	5	1		1	
Parous	35	0.33(0.08-1.29)		0.41(0.09-1.73)	
PreopCA-125			0.05		0.26
<100	22	1		1	
>100	18	3.10(0.99-9.65)		2.09(0.57-7.26)	
ES			0.25		0.78
No	25	1		1	
Yes	15	0.49(0.14-1.66)		0.81(0.18-3.62)	
Ascite			0.40		0.50
No	27	1		1	
Yes	13	1.61(0.53-4.94)		1.56(0.42-5.68)	
Resudual tumor			0.27		0.28
>1cm	6	1		1	
<1cm	34	0.48(0.13-1.76)		0.40(0.08-2.10)	
FIGO stage			0.04		0.36
I,II	24	1		1	
III,IV	16	3.27(1.05-10.13)		1.89(0.48-7.44)	
Chemotherapy			0.82		0.40
CP(CAP)	6	1		1	
Paclitaxel +platinum	32	1.30(0.28-5.96)		0.39(0.04-3.24)	
None	2	2.19(0.19-24.8)		2.19(0.09-51.5)	

Cox`sregression analysis (Table 3).

Table 3: *Univariate and multivariate Cox`s regression analysis of clinical variables affecting overall survival for patients with CCC*

Cox`s regression analysis in patients with CCC revealed that the level of preoperative CA-125 was not a significant difference but had a remarkable correlation with overall survival in patients with CCC (P=0.051). The results from the univariate analysis showed that stage was the only prognostic factor for affecting overall survival in patients with CCC. But multivariate analysis showed stage was not an independent prognostic factor. Other covariates (age, parity, pre-op CA-125, ES, ascites, residual tumor, chemotherapy regimen) were not significant prognostic factors according to univariates and multivariate.

The differences in PFS and OS of between the subgroups (residual tumor diameter <1cm group vs. >1cm group) were not statistically significant in patients with stage I & II (P=0.53, P=0.47, respectively) and with stage III & IV (P=0.39, P=0.20, respectively) (Figure was not shown in this article). But, the patients with stage I & II had significantly better PFS and OS than those with stage III & IV. (P<0.01. P=0.03, respectively). Estimated 5-year PFS and OS were 91% and 80% in stage I & II, 36% and 55% in stage III & IV, respectively. Median PFS was 22months, and

median OS was 69months in stages III & IV (Figure 1 & 2).

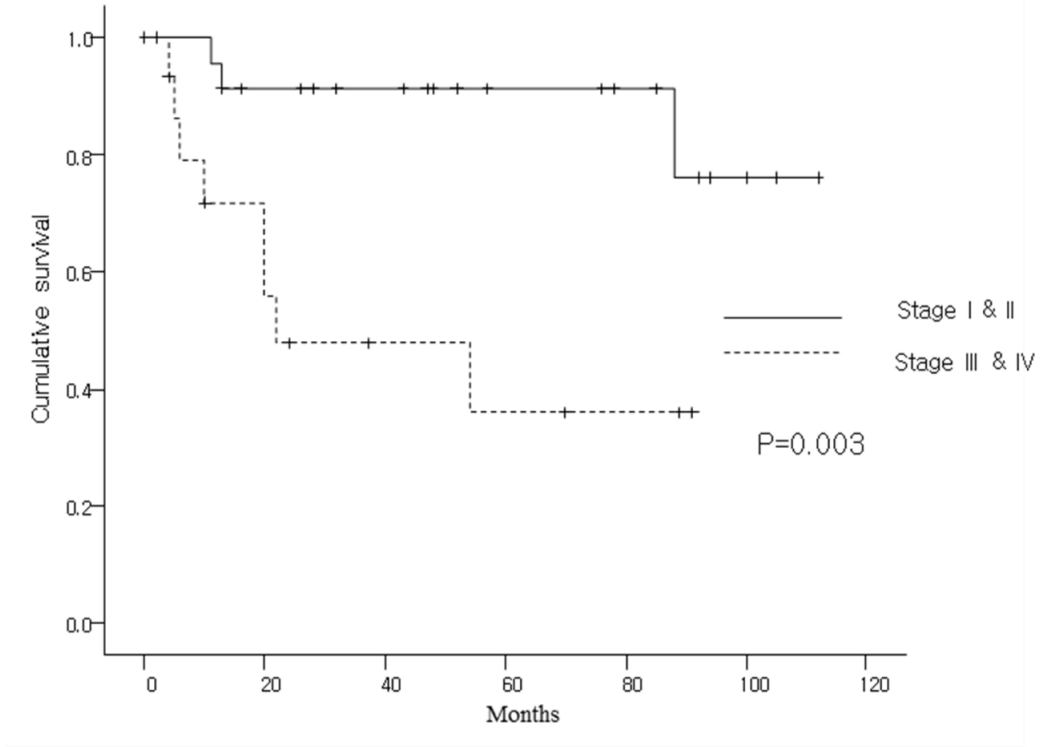

Figure 1: *kaplan- meier estimated progression free survival.*

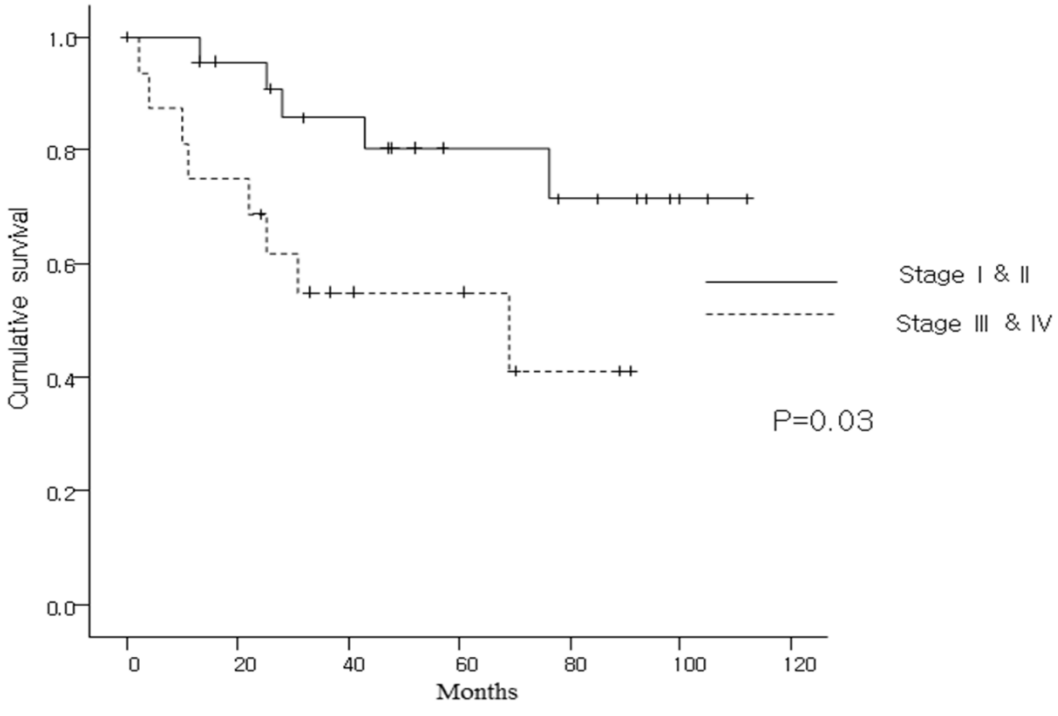

Figure 2: *Kaplan- Meier estimated overall survival.*

Discussion

CCC has been reported to be an interesting histology type classified as a subgroup of epithelial ovarian cancer with unique clinical characteristics [8, 10, 11]. Several studies suggest that CCC of the ovary tended to present at earlier stages. The proportion of stage I/II tumors ranged from 59 to 71% [2, 8, 11, 17]. Our study also supported those reports [stage I & II disease vs. stage III & IV (60% vs. 40%)] especially, among patients with stage I CCC, the majority has stage IC (15/22 in stage I). The present study compared with other reports had a similar finding that CCC was accompanied with endometriosis (37.5%). The association between endometriosis and clear cell or endometrioid ovarian cancer is well documented [18, 19]. Sampson was the first author who described a possible association between ovarian cancer and endometriosis. Since then, several studies have reported a potential malignant transformation of endometriosis in the ovary. The frequency of coexistent endometriosis in patients with CCC ranged from 5~54% [18-22].

The reasons for early-stage detection of CCC may be explained by the slow growing behavior and frequent presentation as relatively large masses and by the fact that endometriosis may be symptomatic, which may lead to an earlier diagnosis of this otherwise silent disease in early stages [23]. In our study of patients with CCC, endometriosis was associated with 37.5% of the clear cell ovarian cancer. Some studies reported that patients having ovarian clear cell carcinoma with pelvic endometriosis exhibited a better prognosis than those without endometriosis [24]. On the contrary, other studies suggested that there are no statistical differences concerning the recurrence or survival [23]. There was no statistical difference regarding overall survival in our study (P=0.25). However, careful attention is required to interpret this result because of the small sample size in the current study.

More than 80% of epithelial ovarian cancers are found in postmenopausal women. The peak incidence of epithelial ovarian cancer is 56 to 60 years of age [25]. However, the incidence age of CCC ranges from 30 to 72 years of age in the current study. This cancer is relatively common in women younger than age 50(62.5%). Especially, there were 8(20%) patients in the fourth decade and 17(42.5%) patients in the fifth decade in our study.

Interestingly, there was a close correlation between the level of CA-125 and survival in the present study, although there was no statistical significance (p=0.051). The serum level of CA-125 is commonly used as the most available diagnostic marker for ovarian cancer. But, the level is relatively low in CCC. Meyer et al reported that 50% of patients with CCA did not show abnormal CA-125 levels [26]. Thus CA-125 measurements cannot often contribute to the detection of ovarian cancer, especially CCC, in the clinic, and this failure may lead to difficulties in providing a proper therapy. Therefore, to achieve a more successful clinical treatment of ovarian cancer, new markers are needed that improve specificity and early detection of CCC. Recently, Morita et al reported that they discovered clinically useful candidates by a proteomic approach [27]. But, there have yet been no reliable biomarker for diagnosis and target therapy.

The rate of optimal debulking (≤ 1cm residual tumor diameter) in the present study was 90% (36/40). But, there was no difference in survival between patients who received optimal and suboptimal cytoreduction (P=0.27 & 0.28 univariate & multivariate analysis, respectively). In general, optimal cytoreduction is a well-known prognostic factor in other subtypes of epithelial ovarian cancers [6, 7]. However, due to the small number of cases (10%, 4/40) in the suboptimal group, we considered that our study showed no significant difference in survival. Therefore, there was a little bit of pitfall for Statistical analysis.

The results from univariate analysis showed that stage was the only prognostic factor for affecting overall survival in patients with CCC. But multivariate analysis showed that stage was not an independent prognostic factor. Such results may be considered due to the high proportion of optimal cytoreduction (≤ 1cm residual tumor diameter) in our study [90 % (36/40)]. Other covariates (age, parity, pre-op CA-125, ES, ascites, residual tumor, chemotherapy regimen) were not significant prognostic factors according to univariates and multivariate Cox`s regression analysis.

For women treated with platinum-based chemotherapy, the overall clinical response rate was 89%, including a CR in 75% (27/36) and a PR in 14% (5/36), to adjuvant chemotherapy. Our study showed a very higher response rate (89%) with platinum-based chemotherapy in CCCs than do the show in other histologic types of epithelial ovarian cancer.it may be due to a relatively large proportion of patients with early stage than other histologic types of epithelial ovarian cancer and a higher rate of optimal debulking surgery (90%). But, there was no survival benefit according to the chemotherapeutic regimen in the patients who received cytoreductive surgery followed in between by conventional platinum-based chemotherapy (CAP or CP) and by paclitaxel and platinum-based chemotherapy (P=0.40). Among patients receiving CP (CAP) chemotherapy in the current study, four patients with stage IA, one patient with stage IB, and another one patient with stage IC. Among Other patients receiving TP (TC) chemotherapy, all patients except one with stage IA were more than stage IC. Combination chemotherapy consisting of a platinum analog and paclitaxel after debulking-surgery is the established standard therapy for advanced ovarian cancer. But, the optimal chemotherapeutic regimen for CCC is still being debated. Clear cell carcinoma is treated in the same manner as other epithelial ovarian carcinomas at our institute, without any particular consideration because of its low rate of incidence among epithelial ovarian carcinoma patients. However, stage IA and IB patients with CCC were treated by CAP (CP) in our institute, because of government `s policy (national health insurance). There have been only a few reports to document the response of chemotherapeutic regimen for CCC patients, but each of them included a relatively small number of cases. The two reports suggested that CAP regimen showed a low response rate and quite a high incidence of PD in CCC patients [6, 11]. Recio et al. demonstrated that platinum-based chemotherapy did not appear to improve the survival of patients with clear cell carcinoma compared to survival of patients given nonplatinum-based chemotherapy. They suggested that platinum-based chemotherapy such as cisplatin, Adriamycin, cyclophosphamide (PAC), or cisplatin and cyclophosphamide (CP) have generally low lacked sensitivity for clear cell carcinoma of the ovary [13]. In support of this conclusion, Gorai et al reported that clear cell carcinoma cells exhibited resistance to cisplatin in vitro study [12]. Ho et al suggested a potential benefit of paclitaxel and carboplatin regimen for stage I clear cell carcinoma in comparison to regimen reported in previous studies [28]. Another study by Ho et al showed that paclitaxel plus platinum-based chemotherapy for improving survival among patients with stage III and IV clear cell carcinoma [16]. Based on their study, they suggested that paclitaxel plus platinum regimen had a higher response rate compared to conventional platinum-based chemotherapy [16]. However, the results by Takano et al showed that there was no survival benefit with chemotherapy with paclitaxel and platinum compared with CAP regimen in both early and advanced cases [6]. Also, our series showed no survival benefit between paclitaxel and platinum and CAP regimen in patients with CCC. The current series might support the results of ACTION study which no benefit of adjuvant chemotherapy was observed in early-stage ovarian cancer with optimal surgical procedures [29], despite CCC or this might be interpreted as like that, due to a very small number of cases in CP (CAP) group. Until now, there is no clinical trial for the treatment of CCC patients of the ovary. Further studies are needed to establish the candidate regimen for CCC of the ovary.

In general, many authors have stated that serous epithelial ovarian cancer has a better prognosis at both early stage and advanced stage than CCC. Omura et al. suggested that the median time to death was 6.7months for the women with CCC compared to 16.4 months for those with stage III & IV serous epithelial ovarian cancer [30]. Also, Goff et al reported that CCC was associated with a poorer outcome, with a median survival of 12months compared to 22 months for serous carcinoma [9]. In contrast, Sugiyama et al. reported that the estimated 5-yr OS for patients with CCC did not differ significantly from that for patients with serous adenocarcinoma [52% in CCC vs 44.1% in SAC] [11]. Also, Kennedy et al. reported that the overall survival for patients with CCC was identical to that for patients with other high-grade epithelial ovarian cancers when controlled for grade and stage [31]. Ryu et al suggested that CCC of the ovary showed 57% overall 5-year survival rate. In stage I disease, 5-year survival rate of CCC of the ovary is comparable to that of other epithelial ovarian cancers (82% versus 85%). However, advanced-stage CCC of the ovary showed an extremely poorer prognosis than the other epithelial ovarian cancers (7% versus 25%), with the stage serving as the strongest prognostic factor [32]. In the present study, CCC of the ovary showed a more favorable prognosis than expected. In our study showed that 5-yr PFS and 5-yr OS of CCC have similar or better than that of other epithelial ovarian cancer. [91% and 80% in stage I & II, 36% and 55% in stages III & IV, respectively in CCC]. Median PFS was 22months, and median OS was 69months in stage III & IV. why there are rather favorable overall survival rates associated with CCC of the ovary may be explained by the relatively large proportion of early-stage disease [60% (24/40)], high proportion of optimal cytoreduction (≤ 1cm residual tumor diameter) [90% (36/40)] and the chemotherapy with paclitaxel plus platinum (cisplatin or carboplatin) which administered to patients with CCC (mainly ≥stage IC) as a main chemotherapy regimen [83%(30/36)].

According to many studies, patients with early-stage CCC have a relatively favorable prognosis than expected, but patients with advanced-stage CCC have a poorer prognosis than do those with other pathological types of epithelial ovarian cancer, because of its chemoresistance and highly invasive character. Therefore, it may be important for the improvement of survival in patients with CCC that early detection and optimal debulking-operation of patients with CCC. Considering the limit of CA-125 that 50% of patients with CCC did not show abnormal CA-125 levels [26], studies for finding of new markers that improve specificity and early detection of CCC are warranted.

Due to the very small number of cases in both stage II and stage IV, Analysis was done divided two subgroups. Therefore, further analysis should be conducted, if a larger number of patients with CCC would be gathered later. But, to my knowledge, until now, among single research institution published papers, our study has the largest number of patients with CCC. Therefore, the method of therapies (surgery or chemotherapy) which was followed at our single institution was more homogeneous than that done at multi-center research so that there may be advantages to analysis and evaluation of the results because of fewer confounding factors. But, clearer information of the clinical characteristics and treatment results in the patients with CCC, a large-scale, multi-center, prospective clinical trial is warranted.

Conclusion

Our results suggest that CCC has a distinct clinical behavior, similar to previous studies, that frequently presents at early- stages and is associated with endometriosis. In addition, there was a close correlation between the level of CA-125 and survival, and there was no survival benefit according to chemotherapeutic differences. 〔CAP (CP) VS TP (TC)〕

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