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Salvage Chemotherapy for Patients With Recurrent or Persistent Ovarian Clear Cell Carcinoma

A Retrospective Study of 164 Cases

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Abstract: The purpose of this study was to evaluate the effects of salvage chemotherapy on recurrent or persistent ovarian clear cell carcinoma (CCC) with the goal of identifying a more rational treatment regimen for this lethal disease.

The medical records of patients with CCC were retrospectively reviewed to select patients that were subsequently treated for recurrent or persistent disease.

Of the 164 women with recurrent or persistent CCC, 485 chemotherapy courses with 1766 cycles were administered. Overall, the clinical benefit rate (CBR) was 39.4%, and the mean progression-free survival (PFS) was 4.5 months. Grade 3/4 toxicities occurred in 94 courses (19.4%). The CBR for TC was 45.1%, with a PFS of 3.7 months. Compared to that of TC, the CBRs for PC and CC were significantly lower ($P = 0.020$ and 0.021, respectively). The CBRs and PFS for PAF-C were slightly higher ($P = 0.518$ and 0.077, respectively), but showed a significantly higher adverse event rate (AER, $P = 0.039$). The CBR for bevacizumab was 50% with an extraordinarily long PFS (49.8 months). Gemcitabine and oxaliplatin had similar values for CBRs (44.4% and 44.1%) and PFS (2.5 and 3.4 months), respectively. Docetaxel (weekly) exhibited a notably low AER of 2.7%, and topotecan was associated with a relatively long PFS (7.7 months).

For cis/carboplatin-pretreated patients, the existing active agents, such as oxaliplatin, gemcitabine, topotecan, and especially bevacizumab, are promising. Docetaxel (weekly) is well tolerated and might offer a particularly viable option for heavily pretreated patients. However, additional research to identify for a continued search for the optimal combination of chemotherapeutics or novel agents is still warranted.

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Abbreviations: AER = adverse event rate, CBR = clinical benefit rate, CCC = clear cell carcinoma, CR = complete remission, CRS = cytoreductive surgery, EOC = epithelial ovarian cancers, FIGO = International Federation of Gynecology and Obstetrics, GCIG = Gynecologic Cancer Intergroup, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PLD = pegylated liposomal doxorubicin, PR = partial response, RR = response rate, SD = stable disease, TFI = treatment-free interval.

INTRODUCTION

Ovarian clear cell carcinoma (CCC) has been recognized as a distinct histological type, accounting for up to 15% of epithelial ovarian cancers (EOC),[1] and the incidence might be even higher among Asian women.[2] CCC is resistant to platinum-based chemotherapy and has a poorer prognosis than other histological types of EOC.[1,3–5] For recurrent or persistent CCC, the response rate (RR) is extremely low, the reported RR is less than 10% even for platinum-sensitive CCC.[6,7] Currently, there is no well-established chemotherapeutic regimen for CCC.

In 2011, the 4th Ovarian Cancer Consensus Conference identified CCC as one of the primary unmet needs in this field and encouraged researchers to identify new treatment strategies for CCC, including alternative chemotherapy regimens.[8] Certain medical groups have risen to this challenge.[9–12] However, the existing studies have been limited by small size and have been unable to arrive at a definitive conclusion. In a previous study,[13] we determined that FIGO (International Federation of Gynecology and Obstetrics) stage and residual disease (>2 cm) were independent predictors of overall survival (OS) and progression-free survival (PFS) for patients with ovarian CCC. This study focuses exclusively on a recurrent or persistent subset of the disease and evaluates the effects of salvage chemotherapy on this target population to identify into a more rational treatment regimen for this lethal disease.

MATERIALS AND METHODS

The medical records of all of the patients with CCC who were diagnosed and treated at Peking Union Medical College Hospital (PUMCH) and Beijing Chao-Yang Hospital between 1993 and 2013 were collected and analyzed. The eligibility criteria included the following: patients whose tumor specimens from the initial surgery were histologically confirmed as pure-type ovarian CCC; patients who underwent cytoreductive

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surgery (CRS) and subsequent systemic chemotherapy as primary treatment; patients who subsequently were treated for recurrent or persistent disease; patients who received at least 2 cycles of salvage chemotherapy with an assessable response; and patients for whom there was adequate clinical information. Patients who were immediately opted for at another hospital after the initial surgery were excluded. Patients suffering from a primary malignant tumor in other parts of the body or from other malignant ovarian cell types were also excluded. The following information was collected and evaluated: age, date and type of primary surgery, stage of disease, completion date of primary chemotherapy, date of first disease progression or recurrence, date of start and completion as well as the number of cycles of each systemic agent for recurrent or persistent disease, patient' response, and disease status at the last contact.

The predominant initial surgical procedure consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and the removal of suspicious nodes. Ascites or washings were routinely collected before surgery, and cytology data were evaluated for all of the patients. Lymphadenectomy was not mandatory. Maximal CRS was performed when a residual tumor remained. Two independent pathologists with extensive experience in gynecologic pathology reviewed all of the pathological slides; these pathologists were blinded to patient outcome. Pure-type CCC was defined as typically clear cells or hobnail cells present in papillary, solid, or tubule-cystic patterns. Mixed-type CCC was defined as the presence of other epithelial cell types and CCC, with each individual epithelial component comprising no less than 10%, as defined by the WHO criteria. Disease staging was performed according to the exact FIGO staging criteria.

Cis/carboplatin-based chemotherapy was administered as the postoperative first-line treatment. The responses to the systemic agents were recorded according to version 1.1 of the Response Evaluation Criteria in Solid Tumors.[14] In the absence of measurable disease, the CA125 level was used to evaluate the response according to the Gynecologic Cancer Intergroup CA125 response criteria.[15] The clinical benefit rate (CBR) was estimated as the rate of the response-evaluable courses of chemotherapy achieving complete remission (CR), partial response (PR), or stable disease (SD). PFS was calculated in months from the time of response to the time of progressive disease (PD).

Adverse events were analyzed according to Common Terminology Criteria for Adverse Events version 4.0. The adverse event rate (AER) was defined as the number of G3/G4 adverse events relative to the number of chemotherapy courses. All of the chemotherapy courses in which at least 1 day of the first cycle was administered were included in the toxicity evaluation.

Relapse was defined by clinical or imaging evidence. The treatment-free interval (TFI) was defined as the time (in months) from the completion of initial therapy to disease recurrence. Retreatment was provided on an individual basis with palliative intentions according to medical comorbidities, oncologist suggestions, and informed consent from the patient. Repeated CRS was performed if the recurrent or persistent tumor was confined to the abdominopelvic cavity and could be safely resected. Salvage chemotherapy was the core treatment for recurrent or persistent disease, and regimens were predominantly chosen based on the patient's sensitivity to cis/carboplatin. Generally, for cis/carboplatin-sensitive patients (TFI ≥ 6 months), cis/carboplatin-based (occasionally including g oxaliplatin) regimens were readministered. For resistant (TFI < 6 months) or persistent disease, nonplatinum regimens comprising several second-line active agents were used. If a patient showed resistance to a nonplatinum regimen in subsequent lines of therapy, platinum-based chemotherapy (mainly oxaliplatin) would be attempted again; conversely, nonplatinum-based chemotherapy would be attempted a second time for patients who were resistant to platinum-based regimens in subsequent lines of therapy. Treatment was continued until a CR was achieved after completing the scheduled courses, PD occurred, or severe toxicity developed. Local radiotherapy was delivered occasionally for repeated recurrent or persistent cases with a palliative intent.

After completing primary or salvage treatment, the women were followed up once a month for the 1st year, every 3 months for the 2nd year, every 6 months during years 3 to 5, and every year thereafter. Efforts were made to contact women by phone or letter who did not attend regular follow-up appointments to obtain the required information. For recurrent disease, OS was calculated from the date of the 1st recurrence to the date of death from toxicity or CCC. For persistent disease, OS was calculated from the date of initial surgery to the date of death from toxicity or CCC.[11] Patients who died of other conditions and surviving patients at the time of their last visit were censored.

Patient records and information were anonymized and deidentified prior to analysis. The study protocol was approved by the ethics committee at PUMCH and Beijing Chao-Yang Hospital, Beijing, China.

Statistical Analysis

All of the statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC). All of the tests were 2 sided, and $P < 0.05$ was considered statistically significant. Chi-square tests or Fisher exact test was performed to compare the CBR and AER between active agents. The number of previous cycles of chemotherapy regimens and PFS was compared using the 2 independent samples *t*-test. The Kaplan–Meier method was used to analyze survival rates.

RESULTS

Clinicopathologic Characteristics

During the study period, 496 consecutive women with ovarian CCC underwent CRS at the 2 hospitals. In total, 35 patients (7.1%) were not followed up immediately after surgery, 19 of whom preferred to continue treatment at hospitals near their residence due to their economic condition or the lack of convenient transportation. The relevant data were not available in the records of the remaining 16 patients. Nineteen patients (3.8%) had other malignancies, including breast cancer (10 patients), cervical cancer (5 patients), and thyroid cancer (4 patients). Sixty-one (12.3%) patients had other malignant histological types in the ovaries, including ovarian endometrioid carcinoma (32 patients), serous cystadenocarcinoma (20 patients), mucous cystadenocarcinoma (2 patients), transitional cell carcinoma (2 patients), and mixed epithelial carcinoma (5 patients). Six (1.2%) patients could not afford chemotherapy after the initial surgery because of serious complications and 5 of these patients died of the disease at the last contact. The FIGO staging of the remaining 375 women was distributed as follows: 180 cases were stage I (Ia: 63, Ib: 4, and Ic: 113), 43 cases were stage II (IIa: 9, IIb: 13, and IIc: 21), 132 cases were stage III, and 20 cases were stage IV. Among these women, 164 developed

recurrent or persistent disease after primary treatment and met the eligibility criteria; therefore, these patients were included in the analysis (Table 1). The mean age at initial diagnosis was 51.4 years. Recurrence occurred in 27 stage I cases, including 6 Ia cases, a single case of Ib and 20 cases of Ic (recurrence rate 15% for stage I overall, 9.5% specifically for stage Ia). There were 15 stage II cases (IIa: 2, IIb: 5, and IIc: 8), with a recurrence rate of 34.9%. For stage III, 102 of 132 cases (77.3%) showed recurrent (76 cases) or persistent (26 cases) disease. All 20 stage IV cases (100%) had recurrent (14 cases) or persistent disease (6 cases). Initial (pelvic and para-aortic) lymphadenectomy was performed in 98 patients (59.8%). Node involvement was present in 40 patients, including 1 woman who had a positive left supraclavicular lymph node and was exempt from lymphadenectomy. After the initial surgery, 37 patients (22.6%) had macroscopically residual disease (residual tumor >1 cm) within the abdominopelvic cavity.

After the completion of platinum-based front-line chemotherapy, the mean TFI for the entire cohort was 10.9 months, and 58% had a TFI of <6 months. A total of 88 (53.7%) women underwent CRS at least once more, and 47 (53.4%) of these women had their abdominopelvic tumors completely re-resected (residual tumor ≤ 1 cm). The sites of recurrent and persistent disease included the abdomen or pelvis (109 patients), liver (49), lymph nodes (21), vaginal stump (20), spleen (19), chest cavity (5), lung (5), and other sites (38).

Response to Salvage Chemotherapy

All 164 patients received second-line regimens, and a fraction of these patients proceeded to third-line, or more

TABLE 1. Clinicopathologic Characteristics of the 164 Patients With Recurrent or Persistent CCC

Parameter		Number of Patient	Percent, %
Age (mean; range)		51.4 ± 10.3; (31–85)	
FIGO stage at diagnosis			
I		27	16.5
II		15	9.1
III		102	62.2
IV		20	12.2
Abdominopelvic residual disease after initial surgery			
≤ 1 cm		127	77.4
>1 cm		37	22.6
Initial lymphadenectomy			
+		98	59.8
−		66	40.2
First line chemotherapy			
Taxane and platinum		79	48.2
Other platinum-based regimen		85	51.8
Disease status at completion of primary chemotherapy			
NED	Stable	132	80.5
Persistent disease	Progressive	25	19.5
		7	
TFI, month (mean; range)		10.9 ± 22.0; (0–156)	
<6		96	58.5
≥ 6		68	41.5
RCRS			
+	Abdominopelvic residual disease ≤ 1 cm	47	53.7
	Abdominopelvic residual disease >1 cm	39	
	Unknown	2	
−		76	46.3
Salvage chemotherapy			
Cis/carboplatin-based regimen		118	72.0
Second-line active agents involved regimen		85	51.8
Radiation therapy			
+		21	12.8
−		143	87.2
OS time, month (mean; range)		22.6 ± 25.0; (1–131)	
Status at the last contact			
NED		14	8.5
AWD		80	48.9
DOD		70	42.7

AWD = alive with disease, DOD = dead of disease, NED = no evidence of disease, OS = overall survival, RCRS = repeated cytoreductive surgery, TC = paclitaxel + carboplatin, TFI = treatment-free interval from first line chemotherapy, TP = paclitaxel + cisplatin.

chemotherapy. The main cis/carboplatin-based salvage chemotherapy regimens consisted of TC (paclitaxel + carboplatin), carboplatin), TP (paclitaxel + cisplatin), TCw, TPw, PC (cisplatin + cyclophosphamide), PAC (cisplatin + adriamycin + cyclophosphamide), CC (carboplatin + cyclophosphamide), or PAF-C (cisplatin + adriamycin + 5-fluorouracil + cyclophosphamide). For TCw, paclitaxel (60–90 mg/m^2 on day 1, weeks 1–6) plus carboplatin (AUC = 5 on day 1, weeks 1 and 4) were administered intravenously every 7 weeks for 3 cycles. For TPw, paclitaxel (80 mg/m^2 on day 1, weeks 1–6) plus cisplatin (70 mg/m^2 on day 1, weeks 1 and 4) were given intravenously every 7 weeks for 3 cycles. For PAF-C, cisplatin (100 mg), adriamycin (300 mg), and 5-fluorouracil (750 mg) were administered intraperitoneally on days 1 and 2, and cyclophosphamide (400 mg) was given intravenously on days 1 and 2; these treatments were performed every 28 days for 3–4 cycles. The predominant second-line active agents used in our series included docetaxel, oxaliplatin, gemcitabine, oral etoposide, topotecan, ifosfamide, pegylated liposomal doxorubicin, thiotepa, mitoxantrone, and bevacizumab. These second-line agents were used without a well-defined regimen, either as single agents or in combination with taxane, platinum, or each other (eg, gemcitabine plus oxaliplatin or carboplatin, docetaxel plus oxaliplatin, or topotecan plus ifosfamide). The protocol for weekly docetaxel treatment was as follows: 40 mg/m^2 intravenously on day 1, weeks 1–3, and every 4 weeks for 3 cycles. The gemcitabine monotherapy protocol consisted of 1000 mg/m^2 intravenously on day 1, weeks 1–3, and every 4 weeks for 4 cycles. The gemcitabine + carboplatin protocol was as follows: intravenous gemcitabine (1000 mg/m^2, day 1, weeks 1–2) and carboplatin (AUC = 4, day 1, week 1) every 4 weeks for 4 cycles. The topotecan monotherapy protocol was such as 4 mg/m^2 intravenously on day 1, weeks 1–3, and every 4 weeks for 4 cycles. The following oxaliplatin protocol was used 130 mg/m^2 intravenously delivered, usually in combination with the other agents.

A total of 485 chemotherapy courses with 1766 cycles were administered, and the mean number of applied previous chemotherapy cycles was 10.5 (Table 2). Overall, patients exhibited PD in 269 courses, a CR in 74, a PR in 51, and SD in 50; 41 courses were not evaluable (Table 3; Figure 1A, B). For the entire series, the CBR was 39.4%, and the mean PFS was 4.5 months. Eight cis/carboplatin-based regimens were predominantly administered. TC was the most common of these regimens, with a total of 89 courses (371 cycles) administered to 78 patients. The CBR for TC was 45.1%, with a PFS of 3.7 months. The CBRs for PC and CC were 22.9% and 10.0%, respectively, which were both significantly lower than that of TC ($P = 0.020$ and 0.021, respectively). The PFS times for these 2 regimens were 1.6 and 0.8 months, respectively, which were slightly

TABLE 2. The Number of Chemotherapy Courses (or Cycles) Administrated for Our Series

Active Agents	No. of Patients	No. of Courses	No. of Cycles	No. of Previous Cycles	*P* Value*
Cis/carboplatin-based regimens					
TC	78	89	371	8.5 ± 6.68	
TP	47	47	173	7.3 ± 4.02	0.455†
TC (weekly)	15	18	60	9.9 ± 4.87	0.404†
TP (weekly)	11	11	27	9.2 ± 3.25	0.731†
PAF-C	51	53	188	9.1 ± 6.18	0.648†
PAC	13	14	49	10.4 ± 10.05	0248†
PC	40	42	159	7.7 ± 7.28	0.664†
CC	10	10	31	8.4 ± 2.30	0.982†
Subtotal	118	284	1058	8.6 ± 6.26	
Second-line active agents involved regimen					
Gemcitabine	22	27	100	14.8 ± 8.80	
Bevacizumab	6	6	21	9.2 ± 4.49	0.190‡
Thiotepa	11	11	43	10.4 ± 7.16	0.306‡
Oxaliplatin	27	34	126	13.3 ± 10.24	0.632‡
Docetaxel (weekly)	34	37	119	11.4 ± 6.38	0.125‡
Topotecan	17	18	70	11.3 ± 5.46	0.134‡
Oral etoposide	23	28	128	13.1 ± 8.10	0.427‡
mitoxantrone	5	6	18	12.2 ± 5.12	0.462‡
PLD	13	14	33	11.5 ± 5.74	0.278‡
Ifosfamide	17	19	33	11.7 ± 8.93	0.327‡,§
Subtotal	87	190	658	12.7 ± 8.0	<0.001§
The others	11	11	50	8.9 ± 4.57	0.856†
Total	164	485	1766	10.5 ± 7.29	0.370
Radiation	21	21	—	12.2 ± 6.22	

CC = carboplatin + cyclophosphamide, PAC = cisplatin + adriamycin + cyclophosphamide, PAF-C = cisplatin + adriamycin + 5-fluorouracil + cyclophosphamide, PC = cisplatin + cyclophosphamide, PLD = pegylated liposomal doxorubicin, TC = paclitaxel + carboplatin, TP = paclitaxel + cisplatin.

* Two-independent-sample *t*-test.

† Compare to TC group.

‡ Compare to gemcitabine.

§ Compare to cis/carboplatin-based regimens.

TABLE 3. Different Response Rate and Duration of Active Agents for Recurrent or Persistent CCC

Active Agents	No. of Courses	Response (n)					RR, %	*P* Value*	CBR, %	*P* Value*	PFS, month	*P* Value†
		CR	PR	SD	PD	UE						
Cis/carboplatin-based regimen												
TC	89	18	10	9	45	7	34.1		45.1		3.7 ± 8.05	
TP	47	6	4	4	26	7	25.0	0.306‡	35.0	0.287‡	2.9 ± 6.82	0.615‡
TC (weekly)	18	4	1	2	11	0	27.8	0.603‡	38.9	0.630‡	3.0 ± 4.33	0.742‡
TP (weekly)	11	4	0	1	6	0	36.4	0.885‡	45.5	0.983‡	1.6 ± 1.91	0.413‡
PAF-C	53	5	11	7	22	8	35.6	0.873‡	51.1	0.518‡	11.3 ± 27.32	0.077‡
PAC	14	0	1	3	7	3	9.1	0.064‡	36.4	0.580‡	1.3 ± 1.85	0.334‡
PC	42	4	2	2	27	7	17.1	0.064‡	22.9	0.020‡	1.6 ± 3.45	0.145‡
CC	10	0	0	1	9	0	0	0.029‡	10.0	0.021‡	0.8 ± 2.53	0.271‡
Subtotal	284	41	29	29	153	32	27.8	–	39.3	–	4.3 ± 16.98	–
Second-line active agents involved regimen												
Gemcitabine	27	6	3	3	15	0	33.3		44.4		2.5 ± 4.08	0.487
Oxaliplatin	34	7	4	4	19	0	32.4	0.935§	44.1	0.980§	3.4 ± 6.03	0.527§
Bevacizumab	6	2	0	1	3	0	33.3	1.000§	50.0	0.805§	49.8 ± 37.09	0.002§
Thiotepa	11	1	3	1	6	0	36.4	0.859§	45.5	0.955§	1.5 ± 2.70	0.473§
Docetaxel (weekly)	37	9	2	3	21	2	31.4	0.874§	40.0	0.725§	3.7 ± 14.20	0.673§
Topotecan	18	2	2	3	11	0	22.2	0.421§	38.9	0.712§	7.7 ± 18.83	0.363§
Oral etoposide	28	3	4	2	17	2	26.9	0.611§	34.6	0.465§	2.2 ± 3.37	0.753§
Mitoxantrone	6	1	0	1	4	0	16.7	0.401§	33.3	0.618§	6.0 ± 10.4	0.171§
PLD	14	1	1	2	10	0	14.3	0.192§	28.6	0.323§	0.9 ± 1.75	0.155§
Ifosfamide	19	1	2	1	11	4	20.0	0.351§	26.7	0.256§	2.4 ± 6.41	0.942§
Subtotal	190	32	21	21	108	8	29.1	–	40.7	–	4.4 ± 17.4	–
The others	11	1	1	0	8	1	20.0	0.349‡	20.0	0.199‡	2.5 ± 7.56	0.670‡
Total	485	74	51	50	269	41	28.2	0.325	39.4	0.904	4.5 ± 17.8	0.510
Radiation	21	8	0	0	13	0	38.1		38.1		7.2 ± 15.0	

CBR = (CR + PR + SD)/(no. of evaluable courses), CR = complete remission, PD = progressive disease, PFS = progression free survival, PR = partial response, RR = (CR + PR)/(no. of evaluable courses), SD = stable disease, UE = unevaluable.

* Chi-square test or Fisher exact test.

† Two-independent-sample *t*-test.

‡ Compare to TC.

§ Compare to gemcitabine.

shorter than that of TC ($P = 0.145$ and 0.271, respectively). Compared to TC, the CBR (51.1%) and PFS (11.3 months) for PAF-C were slightly higher and longer ($P = 0.518$ and 0.077, respectively). The other cis/carboplatin-based regimens, including TP, TCw, TPw, and PAC, all had similar CBRs and PFS times as TC.

In this study, 10 unique second-line active agents were used, involving 87 patients with 190 courses (658 cycles), and the response of 182 of these courses was evaluable (Table 3; Figure 1A, B). The average number of previous chemotherapy cycles was 12.7, which was significantly more than the 8.6 cycles that the cis/carboplatin-based regimens averaged ($P < 0.001$). The CBR for bevacizumab was 50%, with an extraordinarily long PFS (49.8 months). The CBR (45%) for thiotepa was the second highest, but the associated mean PFS was only 1.5 months. Bevacizumab and thiotepa were each administered to only 6 and 11 patients, respectively. In our series, gemcitabine and oxaliplatin had a similar CBR (44.4% and 44.1%, $P = 0.980$), with durations of 2.5 and 3.4 months, respectively. Docetaxel (weekly) was the most commonly used second-line active agent in our series, with 37 courses (119 cycles) showing moderate activity (CBR: 40%, PFS: 3.7 months). The CBR for topotecan was 38.9%, but it was associated with a relatively long PFS (7.7 months).

Local radiotherapy was administered to 21 patients. Among these patients, 8 (38.1%) achieved a CR. Among the remaining 13 patients who experienced PD, 6 showed control of the targeted lesions, but new tumors appeared in other sites.

Adverse Effects of Salvage Chemotherapy

No chemotherapy-related deaths were detected in our series (Table 4; Figure 1C). Overall, grade 3/4 toxicities occurred in 94 courses (19.4%). Hematological grade 3/4 toxicities were the most common, including leukopenia in 30 courses (6.2%), thrombocytopenia in 7 courses (1.4%), and anemia in 6 courses (1.2%). There were 15 (16.9%) grade 3/4 adverse events, identified in the 89 courses of TC. The AER for PAF-C was 32.1%, which was significantly higher than that of TC ($P = 0.036$). The AER for gemcitabine was 25.9%. The AERs for oxaliplatin, topotecan, and thiotepa were similar, 20.6%, 22.2%, and 18.2%, respectively, to those of gemcitabine ($P = 0.622$, 0.776, and 0.604, respectively). Docetaxel (weekly) was well tolerated; only 1 case of leukopenia (grade 3) occurred in 37 courses (2.7%). No serious side effects were associated with bevacizumab.

Five out of 21 patients developed an intestinal obstruction related to radiotherapy. Four of these patients (19.0%)

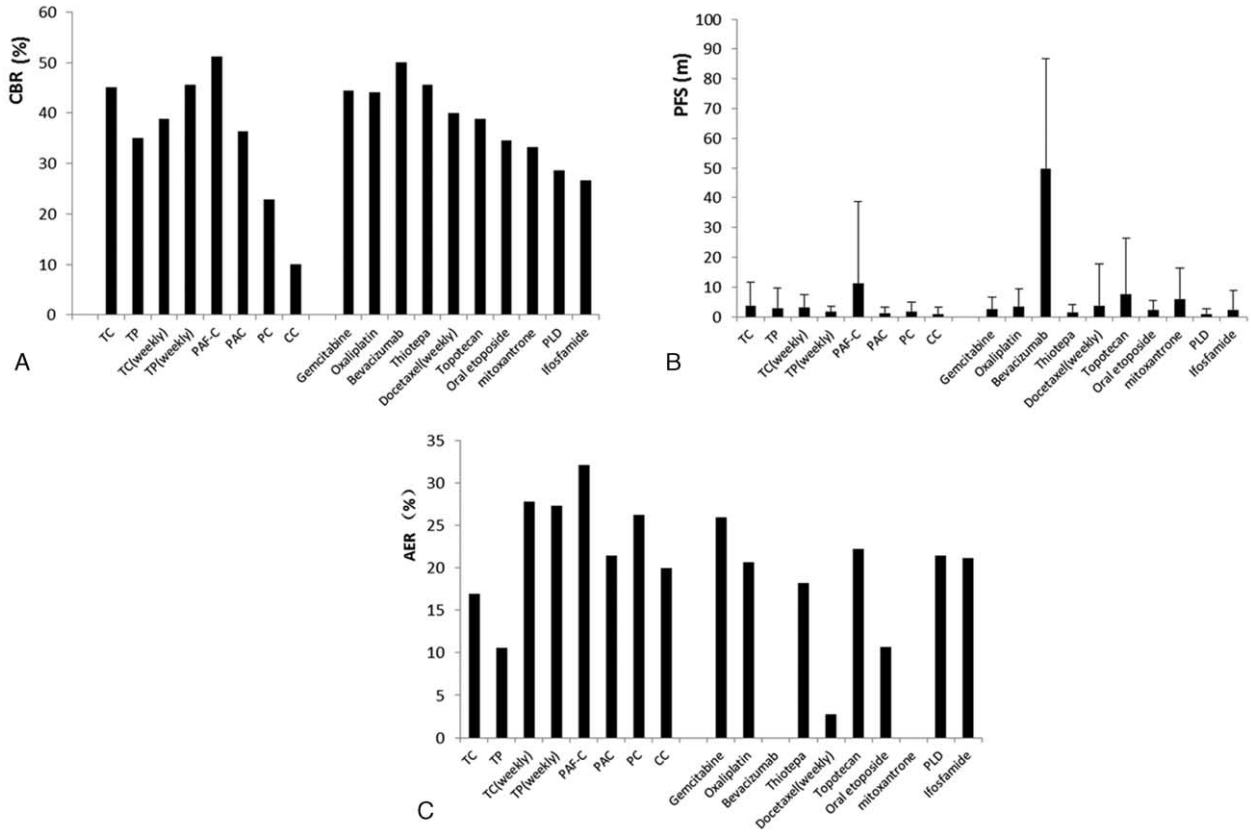

FIGURE 1. The different activity and toxicity of active agents for recurrent or persistent CCC (clear cell carcinoma). (A) The different CBR (clinical benefit rate) of active agents. (B) The PFS (progression free survival) duration (mean, SD) of active agents. The CBR of TC was 45.1% with a PFS of 3.7 months. The CBRs of PC and CC were both significantly lower than that of TC ($P = 0.020$ and 0.021, respectively) with a slightly shorter PFS (progression free survival). Compared to TC, the CBR and PFS of PAF-C were slightly higher and longer. The CBR of bevacizumab was 50%, with an extraordinarily long PFS (49.8 months). The CBR of thiotepa was the second highest, but the associated mean PFS was only 1.5 months. Gemcitabine and oxaliplatin had similar CBRs (44.4% and 44.1%, respectively), with durations of 2.5 and 3.4 months, respectively. Docetaxel (weekly) showed a moderate activity and the CBR of topotecan was 38.9%, but was associated with a relatively long PFS (7.7 months). (C) The different adverse event rate (AER) of active agents for recurrent or persistent CCC. The AER of PAF-C (32.1%) was significantly higher than that of TC ($P = 0.036$). The AERs of gemcitabine, oxaliplatin, and topotecan were similar, 25.9%, 20.6%, and 22.2%, respectively. Docetaxel (weekly) was well tolerated with a 2.7% AER, which was significantly lower than that of gemcitabine ($P = 0.004$). No serious side effects were identified found related to bevacizumab.

underwent an enterectomy with anastomosis, and 1 was alive with short bowel syndrome at the time of last contact.

Status at Last Contact

The mean follow-up period was 37.6 months. At last contact, 70 patients (42.7%) had died of the disease (Table 1), 80 were alive but had tumors, and 16 of the patients had end-stage cancer. Only 14 patients (8.5%) survived without any evidence of a tumor. For the entire group, the mean OS was 22.6 months. The 5- and 10-year OS rates were 41.8% and 23.9%, respectively (Figure 2). The independent predictor for OS included residual tumor and TFI ($P = 0.007$ and 0.015, respectively).

DISCUSSION

Very few reports have described the medical treatment of ovarian CCC due to the relative rarity of this disease.[16] Despite this, CCC is well-known as one of the most aggressive and malignant tumors with a poorer clinical outcome than other types of EOC.[1,3–5] In the presence of recurrent and persistent disease, the patient prognosis is even less promising. In 2010, Gynecologic Cancer Intergroup initiated a meta-analysis and demonstrated that the median OS for stage III/IV CCC was only 21.3 months.[17] For recurrent CCC, the 5-year OS rate was 22.5%, and the mean OS was 25.3 months, according to Kajiyama study.[18] In Yoshino study, the OS was calculated from the date of first recurrence, rather than the date of primary surgery, and the median OS for CCC in the recurrent or persistent setting was only 8 months.[11] In an effort to explore the role of salvage chemotherapy on the survival of the target population, we referred to Yoshino definition. For this study, the mean OS was 22.6 months, and the 5-year OS rate was up to 41.8%. This slight increase might be primarily attributed to the relatively complete follow-up of our series, whereas our treatment strategies possibly played a secondary role.

The majority of the patients in our series were heavily pretreated; the average number of previous cycles of

TABLE 4. Grade 3/4 Toxicity Evaluated by Common Terminology Criteria for Adverse Events v3.0 (n = 164)

		Adverse Effect				
Active Agents	**No. of Courses**	**No.**	**Details**		**AER, %**	***P* Value***
Cis/carboplatin-based regimens						
	TC	89	15	Leukopenia: 8; thrombocytopenia:1; anemia:1; renal dysfunction:1; liver dysfunction: 1; allergy: 2; septicemia:1	16.9	
	TP	47	5	Leukopenia: 1; renal dysfunction:2; nausea and vomiting:1; neuropathy, sensory:1	10.6	0.330†
	TC (weekly)	18	5	Leukopenia:3; thrombocytopenia:1; renal dysfunction:1	27.8	0.298†
	TP (weekly)	11	3	Leukopenia:1; renal dysfunction:1; nausea and vomiting:1	27.3	0.419†
	PAF-C	53	17	Leukopenia:4; thrombocytopenia:1; anemia:1; renal dysfunction:4; nausea and vomiting:2; fever:3; liver dysfunction:1; fatigue:1	32.1	0.036†
	PAC	14	3	Leukopenia:1; anemia:1; nausea and vomiting:1	21.4	0.675†
	PC	42	11	Leukopenia:3; renal dysfunction:3; nausea and vomiting:3; liver dysfunction:1; pain:1	26.2	0.211†
	CC	10	2	Thrombocytopenia:1; hematuria:1	20.0	0.806†
Second-line active agents involved regimen						
	Gemcitabine	27	7	Leukopenia:2; thrombocytopenia:1; anemia:1; neuropathy, sensory:2; mucositis, oral cavity:1	25.9	
	Oxaliplatin	34	7	Leukopenia:2; renal dysfunction:1; neuropathy, sensory:2; fever:1; liver dysfunction:1	20.6	0.622‡
	Bevacizumab	6	0	0	0	0.302‡
	Thiotepa	11	2	Thrombocytopenia:2	18.2	0.604‡
	Docetaxel (weekly)	37	1	Leukopenia:1	2.7	0.004‡
	Topotecan	18	4	Leukopenia:2; anemia:1; liver dysfunction:1	22.2	0.776‡
	Oral etoposide	28	3	Anemia:1; nausea and vomiting:1; constipation:1;	10.7	0.139‡
	Mitoxantrone	6	0	0	0	0.301‡
	PLD	14	3	Neuropathy, sensory:1; mucositis, oral cavity:1; fatigue:1	21.4	0.749‡
	Ifosfamide	19	4	Leukopenia:2; renal dysfunction:1; fever:1	21.1	0.701‡
The others	11	2		Renal dysfunction:1; Allergy:1	18.2	0.913‡
Total	485	94		Leukopenia:30; thrombocytopenia:7; anemia:6; renal dysfunction:15; nausea and vomiting:9; neuropathy, sensory:6; fever:5; liver dysfunction:5; allergy:3; mucositis, oral cavity: 2; fatigue:2; pain:1; constipation:1; hematuria:1 septicemia:1	19.4	0.970
Radiation	21	4		Intestinal obstruction:4	19.0	

AER = adverse event rate = (number of adverse event/number of course), PAC = cisplatin + adriamycin + cyclophosphamide, PAF-C = cisplatin + adriamycin + 5-fluorouracil + cyclophosphamide, PLD = pegylated liposomal doxorubicin, TC = paclitaxel + carboplatin, TP = paclitaxel + cisplatin.

* Chi-square test or Fisher exact test.

† Compare to TC group.

‡ Compare to gemcitabine.

chemotherapy was 10.5. After primary treatment, 3 courses or 10.8 cycles of salvage chemotherapy were administered per capita. Certain patients had undergone repeated CRS or local radiotherapy. Experiences with or lessons learned from these complex treatment procedures might help improve patient prognosis in the future. However, the RR and CBR in the recurrent and persistent setting were extremely low in our series (27.5% and 39.1%, respectively), with a PFS of 4.5 months. In the cis/carboplatin-based subgroup, the RR was 27.8%, which is much lower than the RR of 50% to 90% reported for platinum-sensitive disease for all types of EOC.[19] Eight cis/carboplatin-based regimens were administered in this study. For the paclitaxel/carboplatin doublet (TC) chemotherapy regimen, the CBR was 45.1% with a PFS of 3.7 months, and the AER was 16.9%. Compared to TC, both PC and CC had significantly lower CBRs but slightly higher AERs. PAF-C was slightly higher than TC

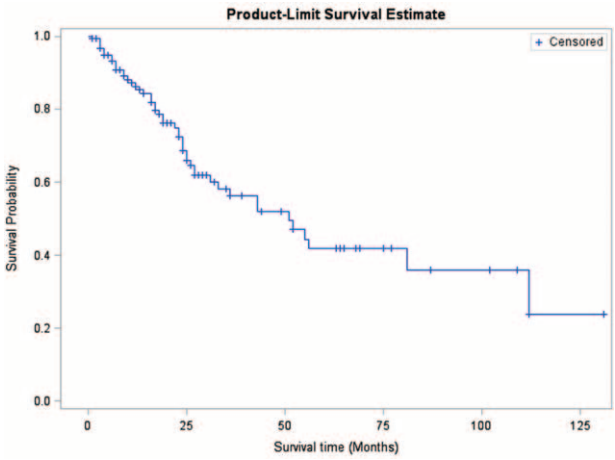

FIGURE 2. The mean OS (overall survival) time was 22.6 months for the entire group. The 5- and 10-year OS rates, respectively, were 41.8% and 23.9%.

based on either CBR or PFS but was associated with significant severe toxicity. Prior to application of this regimen on certain patients, carefully weighing the potential clinical benefits and toxicity is mandatory. The other platinum-based regimens, including TCw, TPw, and PAC, all had similar CBRs and PFSs to those observed for TC. Thus, an improved regimen is still not available to replace the platinum/taxane regimen as the preferred treatment for recurrent or persistent platinum-sensitive CCC.

Oxaliplatin exhibits activity against cis/carboplatin-pretreated ovarian cancers.[20] The weekly administration of oxaliplatin, gemcitabine, and bevacizumab is effective for patients with recurrent and refractory ovarian cancer, and the CBR was as high as 79% with a PFS of 4.4 months.[21] In our series, oxaliplatin showed moderate activity in pretreated recurrent or persistent CCC; the CBR was 44.1%, and the PFS was 3.4 months. This agent could be a candidate for further treatment of ovarian CCC. Gemcitabine, a synthetic nucleoside analog of cytidine, inhibits the S-phase of the cell cycle. Preclinical studies have shown that gemcitabine-based combinations increase cytotoxicity and can potentially overcome drug resistance. These characteristics make gemcitabine an attractive partner for combinations with other cytostatic agents.[22] Several studies have confirmed its efficacy in treating platinum-resistant or platinum-sensitive recurrent ovarian cancer.[23–26] In Yoshino study, the CBR of gemcitabine monotherapy for recurrent or persistent CCC was as high as 60% (3/5).[11] In contrast, the CBR was only 22.2% (2/9) in Crotzer study.[6] In this series, 22 patients received 27 courses (100 cycles) involving gemcitabine, and the CBR was 44.4%, which falls between the previously reported values.

In this present study, bevacizumab was administered to 6 patients with a CBR of 50%. Two of these patients that achieved a CR received combination chemotherapy with PAF-C. As an angiogenesis inhibitor, bevacizumab in combination with chemotherapy has demonstrated significant clinical benefit in both first-line and salvage treatment[27–29] of ovarian cancer. Based on our data, thiotepa exhibited the next best CBR (45%) after bevacizumab. Thiotepa has the beneficial effects of controlling ascites and preventing the recurrence of ovarian cancer.[30,31] Although it has been widely utilized to treat other malignancies,[32–34] gynecologic oncologists have paid little attention to this agent for over 10 years, possibly due to the dominance of the standard chemotherapy, platinum/taxane, in ovarian cancer. However, bevacizumab and thiotepa were administered to only 6 and 11 patients in our series, respectively. The activity of these 2 drugs, especially bevacizumab for the treatment of CCC, deserves further investigation.

A GOG phase II study of docetaxel in paclitaxel-resistant ovarian cancer demonstrated an RR of 22.4%,[35] and weekly docetaxel monotherapy exhibited both activity and tolerability for recurrent ovarian cancer.[36–38] Divided-dose docetaxel might elicit unique anti-angiogenic properties and have improved tolerability when compared to single-dose infusions.[39–41] To the best of our knowledge, the efficacy of weekly docetaxel monotherapy in recurrent or persistent CCC has not yet been reported. In the present series, a total of 35 evaluable courses (117 cycles) of this regimen were administered to 28 patients. Patients showed a CR in 6 courses, a PR in 2, and a SD in 6, resulting in a 40.0% CBR, which closely mirrors the CBR of gemcitabine and oxaliplatin. Notably, this regimen was well tolerated. Only 1 (2.4%) grade 3 leukopenia occurred in the 41 courses of docetaxel (weekly), and no course was delayed due to serious toxicity. This finding is very significant for patients who were heavily pretreated, allowing them to maintain quality of life without significantly sacrificing efficacy.

According to our data, the CBR for topotecan was 38.9%, which is slightly lower than gemcitabine but was associated with a relatively long PFS (7.7 months). The other active agents included oral etoposide and mitoxantrone, both of which had similar activity and toxicity in patients with recurrent or persistent CCC; however, the CBRs of pegylated liposomal doxorubicin and ifosfamide were slightly lower.

The strengths of this analysis were its large sample size and mostly complete follow-up information. However, there were several limitations associated with the retrospective nature of this study, such as potential referral bias, other types of selection bias, and the inclusion of various treatments, doses, and schedules. Consequently, the assessments of the activity and toxicity of the active agents might not accurately represent real conditions. In addition, diverse chemotherapy regimens and active agents were used in this study, because to date, a consensus for a standard cancer chemotherapy regimen to treat recurrent and persistent CCC has not been established. The numbers of patients treated with each individual agent were simply too small to reach statistical significance when compared. This is especially true for third line treatment or beyond.

Despite these limitations, our findings provide important clues for identifying superior therapies for ovarian CCC. For cis/carboplatin-pretreated patients, the existing active agents, such as oxaliplatin, gemcitabine, and topotecan, seem promising. Bevacizumab in particular deserves further investigation. Docetaxel (weekly) exhibits moderate activity and is well tolerated; therefore, it might offer a particularly viable option for this patient population, specifically for heavily pretreated women. However, a preferred regimen replacing platinum/taxane is still not available for recurrent or persistent platinum-sensitive CCC, and a continued search for the optimal combination of chemotherapeutics or novel agents is still required.

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