chemotherapy and other elements of recurrence status for the 13 recurrent or refractory cases are summarized in Table 2.

Response to PTX-PLT chemotherapy among all patients is shown in Table 3. Of the 28 patients, 11 women (39.3%) responded to the combination. The RR for primary disease cases was 53.3% (8/15) in contrast to 23.1% (3/13) for recurrent disease cases. Progressive disease was documented in six cases of primary disease (40%) and nine cases of recurrent disease (69.2%). The RR for cases of late recurrent disease (>12 months) was 20% (1/5), whereas RR for cases of early recurrent (<12 months) or refractory disease was 25% (2/8).

Median survival time in patients with primary CC and recurrent CC was 20 and 28 months, respectively.

Table 3. Clinical Response to chemotherapy

Status	Total	CR	PR	SD	PD	RR (95% CI)
Primary	15	5	3	1	6	53.3% (26.6–78.7)
Recurrence	13	0	3	1	9	23.1% (5–53.8)
Early (<12 months)	8	0	2	0	6	25% (3.2–65.1)
Late (>12 months)	5	0	1	1	3	20% (0.5–71.6)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Discussion

A number of previous studies support the concept that CC demonstrates clinical behavior that is distinct from that of other epithelial ovarian carcinomas, particularly in terms of its chemoresistance and poor prognosis with advanced disease[11,17,19,20]. However, this fact has not been regarded as a serious issue clinically because CC is relatively rare among epithelial ovarian cancer and approximately 60% of CC cases are diagnosed as stage I disease[17,21], which means that only a small percentage of patients with this specific neoplasm require chemotherapy for residual disease. These characteristic features of CC make it difficult to evaluate real response to chemotherapy, and there have been no large prospective studies targeted exclusively at CC patients. In the present study, we retrospectively analyzed response to PTX-PLT chemotherapy among CC patients who had measurable residual disease. Also, to exclude interobserver differences between institutions, histologic types of all surgical specimens were confirmed by central pathologic review and residual disease was reevaluated by Response Evaluation Criteria in Solid Tumors criteria.

To our knowledge, few clinical studies have evaluated response to PLT-based chemotherapy in patients with measurable residual CC. Goff *et al.*[19] reported a higher rate of progressive disease with PLT-based chemotherapy in CC patients with measurable or nonmeasurable disease (16/23; 70%) compared with patients with serous adenocarcinoma (10/34; 29%). Sugiyama *et al.*[17] compared CC patients with stage III disease with serous adenocarcinoma patients with stage III disease using cyclophosphamide–PLT combination chemotherapy with or without doxorubicin. The RR to PLT-based chemotherapy in patients with CC was significantly lower than that in patients with serous adenocarcinoma (RR in CC patients, 11.1%). Although the two reports analyzed CC patients with measurable disease, the combination chemotherapy used for their patients did not include PTX. Recently, Enomoto *et al.* presented the results of a study on PTX-CBDCA combination chemotherapy for epithelial

Table 2. Summary of data for cases of recurrent or refractory disease

Case	Stage	Recurrence site	Previous regimen	Time to recurrence	Therapy effect
1	IC	Lung	CDDP, CPM, ADR	>12 months	SD
2	IC	Para-aortic LN	CDDP, CPM, ADR	<12 months	PR
3	IC	PC	CDDP, CPT-11	<12 months	PD
4	IIIC	Pelvic cavity	PTX, CBDCA	<12 months	PR
5	IC	Lung	MMC, VP-16, CDDP	<12 months	PD
6	IA	Para-aortic LN	CDDP, CPM, ADR	<12 months	PD
7	IIC	Abdominal cavity	PTX, CBDCA	<12 months	PD
8	IIC	Abdominal cavity	CDDP, CPM	>12 months	PR
9	IV	Lung	CDDP, CPM, ADR	>12 months	PD
10	IC	Abdominal cavity	CDDP	<12 months	PD
11	IIC	PC	PTX, CBDCA	<12 months	PD
12	IC	Para-aortic LN	PTX, CBDCA	>12 months	PD
13	IIC	Abdominal cavity	PTX, CBDCA	>12 months	PD

LN, lymph nodes; PC, peritonitis carcinomatosa; CPM, cyclophosphamide; ADR, adriamycin; MMC, mitomycin C; VP-16, etoposide; SD, stable disease; PR, partial response; PD, progressive disease.

ovarian cancer at the 2003 ASCO meeting[24]. This group concluded that CC (RR, 22%) was not as sensitive to the chemotherapy combination as serous adenocarcinoma (RR, 81%). This appeared to be especially true for women with measurable disease, although the authors analyzed only nine such CC cases. On the other hand, Behbakht *et al.* reported on six stage III/IV CC patients with measurable residual tumor, 67% (4/6) of whom partially responded to PTX-PLT[20]. In contrast to previous studies on conventional PLT-based chemotherapy without PTX, the RR for primary residual CC in our study was relatively high (53.3%), although this rate was lower than the 73% RR found in suboptimal patients with advanced ovarian cancer including serous adenocarcinoma[5]. RR for PLT-refractory disease or early (<12 months) recurrent disease and late (>12 months) recurrent disease was 25% and 20%, respectively, in our study. Guastalla *et al.* reported RRs for PLT-refractory patients and those with early (≥3 and <12 months) and late (>12 months) relapsing disease as 24%, 33%, and 70%, respectively. The RR in our study on limited CC patients was lower than those given in previous reports on patients with previously treated advanced ovarian cancer, especially in cases of late recurrent disease[25].

In the present study, median survival time in patients with primary CC disease was 20 months. Sugiyama *et al.* reported that median survival time in primary stage III CC patients treated with PLT-based chemotherapy was 12.7 months. In previous reports for total primary advanced epithelial ovarian cancers including serous adenocarcinoma treated with PTX-PLT, median survival time was 38 months[5]. Our study suggests that RR for primary residual CC was relatively high and median survival time was slightly longer than that reported for stage III CC patients treated with PLT-based chemotherapy, but not as long as survival times given in reports including other histologic types such as serous adenocarcinoma. We conclude that chemosensitivity of CC may not contribute too much to survival. However, it is noteworthy that a significant proportion of CC patients with primary disease responded to PTX-PLT combination chemotherapy. Guastalla *et al.* reported that in recurrent ovarian cancer treated with PTX-PLT, median survival time was 14 months[26]. In the present study, median survival time in patients with recurrent disease was longer (28 months) than in patients with primary disease in spite of a lower RR (23.1% for recurrent disease vs 53.3% for primary disease). We speculate that most patients with recurrent disease in our study were stage I or II and may have had slow-growing carcinoma. This characteristic may be related to the chemoresistance (RR 20%) seen in late recurrent serous adenocarcinoma, a tumor that is generally chemosensitive.

In *in vitro* studies, Ohta *et al.*[26] reported that cyclophosphamide was more effective against serous adenocarcinoma cells than CC cells, whereas PTX was effective against CC cells and ineffective against serous adenocarcinoma cells. Cloven *et al.*[27] reported clear cell tumors had the lower rates of the Extreme Drug Resistance assay to PTX and cyclophosphamide than papillary serous tumors. In addition, Itamochi *et al.*[28] demonstrated that PTX and camptothecin (CPT-11) were effective against three of five CC cell lines while only one CC cell line was sensitive to CDDP. Thus, they concluded that PTX and CPT-11 may be effective agents against CC. In a clinical trial, Shimizu *et al.*[16] reported that chemotherapy including CPT-11 demonstrated significant activity (RR, 52%) in PLT-refractory CC patients, and they advocated that CPT-11 should be given as front-line chemotherapy for CC patients. Our present clinical data also support the *in vitro* studies; the relatively high RR observed in our study seems to be accounted for by the addition of PTX to the chemotherapy regimen. Together with our clinical data, PTX may have the potential to play a key role in the treatment of CC even though chemosensitivity may be lower than that of serous adenocarcinoma. The main limitation of the current study was that the number of cases was too small and the follow-up period too short to form definite conclusions about the contribution of PTX-PLT combination chemotherapy to survival. We speculate that therapy with only PTX may be not sufficient to get better response and prognosis, so new combinations such as PTX and CPT-11 with or without PLT may be considered for future clinical trials.

However, our results with CC patients do indicate that the combination of PTX and PLT has some efficacy compared with conventional PLT-based chemotherapy for this population, and there seem to be some candidates for alternative regimens to improve treatment. A large-scale, prospective trial may be necessary in order to confirm our observation.

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References

1 Akahira J, Yoshikawa H, Shimizu Y *et al.* Prognostic factors of stage IV epithelial ovarian cancer: a multicenter retrospective study. *Gynecol Oncol* 2001;**81**:398–403.
2 Del Campo JM, Felip E, Rubio D *et al.* Long-term survival in advanced ovarian cancer after cytoreduction and chemotherapy treatment. *Gynecol Oncol* 1994;**53**:27–32.
3 Omura GA, Brady MF, Homesley HD *et al.* Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the Gynecologic Oncology Group experience. *J Clin Oncol* 1991;**9**: 1138–50.
4 Fanning J, Bennett TZ, Hilgers RD. Meta-analysis of cisplatin, doxorubicin, and cyclophosphamide versus cisplatin and cyclophosphamide chemotherapy of ovarian carcinoma. *Obstet Gynecol* 1992; **80**:954–60.
5 McGuire WP, Hoskins WJ, Brady MF *et al.* Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;**334**:1–6.
6 The ICON and AGO Collaborators. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;**361**:2099–106.
7 Dizon DS, Hensley ML, Poynor EA *et al.* Retrospective analysis of carboplatin and paclitaxel as initial second-line therapy for recurrent epithelial ovarian carcinoma: application toward a dynamic disease state model of ovarian cancer. *J Clin Oncol* 2002;**20**:1238–47.
8 Rose PG, Fusco N, Fluellen L *et al.* Second-line therapy with paclitaxel and carboplatin for recurrent disease following first-line therapy with paclitaxel and platinum in ovarian or peritoneal carcinoma. *J Clin Oncol* 1998;**16**:1494–7.
9 Serov SF, Scully RE, Sobin LH. *International histologic classification of tumors. No. 9. Histologic typing of ovarian tumors.* Geneva, Switzerland: World Health Organization, 1973.
10 Aure JC, Hoeg K, Kolstad P Mesonephroid tumors of the ovary: clinical and histopathologic studies. *Obstet Gynecol* 1971;**37**:860–7.
11 Kennedy AW, Biscotti CV, Hart WR, Webster KD. Ovarian clear cell adenocarcinoma. *Gynecol Oncol* 1989;**32**:342–9.
12 Crozier MA, Copeland LJ, Silva EG *et al.* Clear cell carcinoma of the ovary: a study of 59 cases. *Gynecol Oncol* 1989;**35**:199–203.
13 O'Brien ME, Schofield JB, Tan S *et al.* Clear cell epithelial ovarian cancer (mesonephroid): bad prognosis only in early stages. *Gynecol Oncol* 1993;**49**:250–4.
14 Sugawa T, Umesaki N, Yajima A *et al.* A group study on prognosis of ovarian cancer. *Acta Obstet Gynaecol Jpn* 1992;**44**:827–32.
15 Ueki M. Report of gynecologic cancer in Japan. *Acta Obstet Gynaecol Jpn* 2001;**53**:1038–48.
16 Shimizu Y, Umezawa A, Hasumi K. A phase II study of combined CPT-11 and mitomycin C in platinum refractory clear cell and mucinous ovarian carcinoma. *Ann Acad Med Singapore* 1998;**27**: 650–6.
17 Sugiyama T, Kamura T, Kigawa J *et al.* Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. *Cancer* 2000;**88**:2584–9.
18 Recio FO, Piver MS, Hempling RE, Driscoll DL. Lack of improved survival plus increase in thromboembolic complications in patients with clear cell carcinoma of the ovary treated with platinum versus nonplatinum-based chemotherapy. *Cancer* 1996;**78**:2157–63.
19 Goff BA, Sainz dela Cuesta R, Muntz HG *et al.* Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease. *Gynecol Oncol* 1996;**60**:412–7.
20 Behbakht K, Randall TC, Benjamin I *et al.* Clinical characteristics of clear cell carcinoma of the ovary. *Gynecol Oncol* 1998;**70**:255–8.
21 Jenison EL, Montag AG, Griffiths CT *et al.* Clear cell adenocarcinoma of the ovary: a clinical analysis and comparison with serous carcinoma. *Gynecol Oncol* 1989;**32**:65–71.
22 Ho CM, Chien T-Y, Shih B-Y, Huang S-H. Evaluation of complete surgical staging with pelvic and para-aortic lymphadenectomy and paclitaxel plus carboplatin chemotherapy for improvement of survival in stage I ovarian clear cell carcinoma. *Gynecol Oncol* 2003; **88**:394–9.
23 Therasse P, Arbuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;**92**:205–16.
24 Enomoto T, Kuragaki C, Yamasaki M *et al.* Is clear cell carcinoma and mucinous carcinoma of the ovary sensitive to combination chemotherapy with paclitaxel and carboplatin? *Proc ASCO* 2003; **20**:447.
25 Guastalla JP, Pujade-Lauraine E, Weber B *et al.* Efficacy and safety of the paclitaxel and carboplatin combination in patients with previously treated advanced ovarian carcinoma. A multicenter GINECO (Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens) phase II study. *Ann Oncol* 1998;**9**:37–43.
26 Ohta I, Gorai I, Miyamoto Y *et al.* Cyclophosphamide and 5-fluorouracil act synergistically in ovarian clear cell adenocarcinoma cells. *Cancer Lett* 2001;**162**:39–48.
27 Cloven NG, Kyshtoobayeva A, Burger RA, Yu IR, Fruehauf JP. In vitro chemoresistance and biomarker profiles are unique for histologic subtypes of epithelial ovarian cancer. *Gynecol Oncol* 2004;**92**: 160–6.
28 Itamochi H, Kigawa J, Sultana H *et al.* Sensitivity to anticancer agents and resistance mechanisms in clear cell carcinoma of the ovary. *Jpn J Cancer Res* 2002;**93**:723–8.

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