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Paclitaxel plus Carboplatin Chemotherapy for Primary Peritoneal Carcinoma: A Study of 22 Cases and Comparison with Stage III–IV Ovarian Serous Carcinoma

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Key Words
Primary peritoneal carcinoma · Paclitaxel · Carboplatin

Abstract
The aim of this study was to assess the clinical characteristics and outcome of patients with either primary peritoneal carcinoma (PPC) or ovarian serous carcinoma (OSC) treated with paclitaxel plus carboplatin chemotherapy. We retrospectively identified 22 PPC patients and 55 stage III–IV OSC patients treated between 2002 and 2007. After exploratory laparotomy, all patients received paclitaxel and carboplatin every 3 weeks, with the goal of optimal cytoreduction. There were no statistically significant differences between the PPC and OSC groups with regard to tumor stage, residual tumor after debulking surgery (initial or interval), serum cancer antigen (CA) 125 levels at diagnosis, and completion of first-line chemotherapy. The progression-free survival (PFS) durations were 12.7 months (95% CI, 6.3–18.5) in the patients with PPC and 15.9 months (95% CI, 13.3–18.5) in those with OSC (p = 0.016). However, the median survival durations were 26.5 months (95% CI, 14.6–38.3) in the patients with PPC and 38 months (95% CI, 23.8–53.8) in those with OSC (p = 0.188). Survival was longer for all patients whose CA125 levels normalized to 26 U/ml during and after treatment. Overall survival (OS) of the patients with PPC was similar to that of the patients with OSC, suggesting that management for advanced-stage OSC would be similar to that for PPC. The combination of optimal debulking with paclitaxel plus carboplatin chemotherapy may offer patients the most effective treatment. The CA125 nadir after cytoreductive surgery can be considered a prognostic factor for OS and PFS in patients with PPC.

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Introduction

Primary peritoneal carcinoma (PPC) is histologically and clinically similar to stage III–IV ovarian serous carcinoma (OSC). PPC was first described by Swerdblow in 1959 [1]. It is a malignancy that spreads widely inside the peritoneal cavity involving mostly the omentum with minimal or no ovarian involvement. The following terms are used to describe these tumors: peritoneal mesothelioma, peritoneal papillary serous carcinoma, serous surface papillary carcinoma, and extraovarian peritoneal serous papillary carcinoma. Histopathological, immunohistochemical, and clinical similarities have been observed between PPC and serous epithelial ovarian cancer [2]. Recent molecular and epidemiological studies, however, have shown some differences between these two diseases [3]. The Gynecologic Oncology Group (GOG) has developed criteria to better define PPC: (1) the ovaries are normal in size or enlarged by a benign process; (2) there is greater involvement in the extraovarian sites than on the surfaces of either ovary; (3) microscopically, the ovaries are not involved with the tumor or exhibit only serosal or cortical implants of a dimension of less than 5 × 5 mm, and (4) the histopathological and cytological characteristics of the tumor are predominantly of the serous type. Although the histopathological and clinical features of PPC have been described in several reports [2, 3], the behavior of this disease remains obscure. Treatment of PPC is based on surgical resection associated with adjuvant chemotherapy. The purpose of this study was to compare the clinical findings and outcomes of PPC and stage III–IV OSC patients treated with paclitaxel plus carboplatin chemotherapy.

Methods

The clinical and pathological records of 22 PPC patients and 55 stage III–IV OSC patients who were managed between October 2002 and December 2007 at the Nara Medical University were reviewed retrospectively. The study was approved by the Institutional Review Board. Pathological diagnosis of PPC was based on the inclusionary criteria of GOG for PPC.

Treatment of both PPC and OSC usually included initial surgery followed by adjuvant systemic chemotherapy. All patients received chemotherapy in combination with carboplatin (area under the curve, 6) and paclitaxel (180 mg/m^2) every 3 weeks after the primary surgery. In some cases, if initial surgery was not considered feasible, interval surgery was performed after three cycles of chemotherapy. Surgical debulking and staging usually consisted of peritoneal washings, bilateral salpingo-oophorectomy, total abdominal hysterectomy, omentectomy, and lymphadenectomy. Pelvic and para-aortic lymphadenectomy was included in the standard procedure for patients with good medical status at the end of the debulking surgery and with absence of or very small residual disease (≤1 cm). In patients with larger residual disease and/or poor medical condition at the end of the debulking surgery, lymphadenectomy was omitted.

The patients with PPC were compared with those with OSC for age at diagnosis, serum cancer antigen (CA) 125 levels (U/ml), surgical staging, whether primary or secondary surgery was optimal (residual tumor ≤1 cm) or suboptimal (residual tumor >1 cm), date of tumor recurrence or progression, and patients' condition at the last follow-up. Although there is no official surgical staging system for PPC, all cases of PPC were considered to be equivalent to FIGO stage III or IV ovarian carcinoma. Progression-free survival (PFS) was defined as the number of months in which there was no evidence of disease on pelvic examination and computed tomographic (CT) scanning.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 11.0 software (SPSS Inc., Chicago, Ill., USA). The unpaired Student's t test for continuous variables and either the χ^2 or Fisher's exact test for categorical data were used to evaluate the statistical significance

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of differences in the clinical characteristics between the two groups. For all statistical tests, the level of significance was set at $p < 0.05$. Survival analysis was performed by the Kaplan-Meier method, and statistical significance was determined by the log-rank test.

Results

The characteristics of the two groups of patients are shown in table 1. The differences between the PPC and OSC patients with regard to median age at diagnosis, clinical stage, performance status, pretreatment CA125 level, and CA125 nadir level were not significant. The pretreatment CA125 level ranged from 104 to 12,629 U/ml (median, 638 U/ml) and from 82 to 71,061 U/ml (median, 1,777 U/ml) in the PPC and OSC groups, respectively ($p = 0.099$). There was no significant statistical difference between the two groups for the proportion of the patients with CA125 nadir concentrations <26 U/ml ($p = 0.945$).

Surgical characteristics of the two groups of patients are detailed in table 2. There was no statistically significant difference between the two groups with regard to the timing of debulking surgery. Bilateral salpingo-oophorectomy, hysterectomy, and omentectomy were performed in all OSC and PPC patients during the debulking surgery. Pelvic and para-aortic lymphadenectomies were performed in 14 patients (63.7%) with PPC and 40 patients (72.7%) with OSC. Optimal debulking (residual tumor ≤1 cm) was achieved in a statistically similar percentage of patients. The median number of courses of first-line chemotherapy (total number of courses administered before and after debulking surgery in patients who underwent interval debulking surgery) was 8 (range, 6–9) in the OSC and PPC patients.

The median duration of follow-up was 29.7 months (range, 5.1–93.7) and 38.8 months (range, 3.9–98.7) in the PPC and OSC groups, respectively. The median PFS durations were 12.7 months (95% CI, 6.3–19.1) in the patients with PPC and 15.9 months (95% CI, 13.3–18.5) in those with OSC ($p = 0.016$). The median overall survival (OS) durations were 26.5 months (95% CI, 14.7–38.3) in patients with PPC and 38.8 months (95% CI, 23.8–53.7) in those with OSC ($p = 0.118$).

In the PPC and OSC groups, survival was longer for the patients whose CA125 levels normalized to ≤26 U/ml (our institution's normal range) during and after treatment (fig. 1, fig. 2). These results were statistically significant in both groups ($p < 0.0001$). The median survival durations for the patients with PPC and OSC who had CA125 levels ≤26 IU/ml during and after treatment were 33.6 and 61.5 months and for the patients with CA125 levels >26 IU/ml they were 11.9 and 24.4 months, respectively. No statistically significant ($p > 0.05$) differences in median survival were found between the PPC and OSC patients.

Discussion

The clinical and pathological characteristics of patients with PPC have been previously investigated in published series [2, 3]. PPC is diagnosed in approximately 10% of patients who undergo laparotomy for ovarian carcinoma [4]. It has been reported that the incidence of PPC has increased over the last decade [4]. However, the

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etiology, pathogenesis, cell type of origin, and clinical characteristics of PPC remain obscure. Histologically, the predominant subtype of PPC is papillary serous, but others have also been reported [4]. The most common symptoms of PPC are abdominal pain, distension, and discomfort. Although PPC commonly involves the abdominal and pelvic peritoneum, the omentum and diaphragm are also affected, and one of the key characteristics of this type of tumor is that it diffusely involves only the peritoneal surfaces, with little or no involvement of the ovaries [4]. Consistent with the findings of other studies [4], we found that all the patients with PPC had stage III or IV disease at diagnosis and elevated serum CA125 levels.

Treatment of PPC is based on cytoreductive surgery and platinum-based chemotherapy. Optimal cytoreduction is the primary goal of the surgical procedure. In this study, 12 patients (54.5%) received optimal cytoreductive surgery. The chemotherapeutic regimen used for PPC should be similar to that used in ovarian carcinoma. Use of platinum-based chemotherapeutic regimens improves patients' survival. Long-term survival can be achieved in some patients using paclitaxel plus cisplatin or carboplatin [5]. Dose-dense weekly administration of paclitaxel is another strategy to enhance antitumor activity and prolong survival in ovarian cancer patients. A dose-dense regimen of paclitaxel once a week plus carboplatin every 3 weeks is associated with longer PFS and OS compared with a conventional regimen of paclitaxel and carboplatin given every 3 weeks in women with advanced ovarian cancer and PPC [6]. Therefore, a dose-dense regimen may be a new treatment option in women with PPC.

The median OS rate reported in the present study (26.5 months) is similar to that reported in previous studies [5, 7], in which the median OS varied between 20.0 and 30.0 months. Optimal cytoreductive surgery, defined as cytoreductive surgery resulting in <1.0 cm residual tumors, was achieved in 54.5% of our study population. This rate is consistent with the rates of optimal cytoreductive surgery (defined as ≤2.0 cm residual tumors), which have been reported to vary between 33 and 69% by other investigators [7–9]. Several comparative and case-control studies seem to have suggested that PPC and OSC have similar prognoses [4, 10], whereas other series have suggested poorer survival in PPC [8]. In our study, PFS was significantly greater in the OSC patients than in the PPC patients, although OS was similar in both groups. However, the reason for the difference in PFS between the two groups was obscure, and the percentage of patients who underwent debulking surgery after neoadjuvant chemotherapy (because of massive unresectable disease during initial surgery) was higher in the PPC group than in the OSC group (90.9 vs. 70.9%). This may indicate that peritoneal spread is more extensive in PPC than in OSC, and we found that PFS is poor in the PPC group. However, the percentage of optimal debulking surgery (residual tumor ≤1 cm) was the same in both groups. Therefore, further studies are needed to determine the survival rates between the two groups. The median follow-up duration in the patients with PPC was shorter than that in the patients with OSC, although the difference was not significant. This may be related to the tendency toward overall shorter survival in the patients with PPC than in patients with OSC.

The CA125 serum concentration has been established as a tool of great importance in the diagnosis of and prognosis for OSC and monitoring of treatment [11]. Several reports have recently indicated that it may be possible to define the risk of relapse and death by dividing OSC patients that have achieved a complete response after primary

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treatment into arbitrary groups based on the CA125 nadir [12, 13]. Values ≤10–12 IU/ml have been associated with increases in PFS [12, 13] and OS [12, 13]. In PPC patients, serum CA125 levels are reported to be elevated in most PPC patients [14, 15]. In our group of PPC patients, OS was longer in those whose CA125 levels normalized to ≤26 U/ml during and after treatment. In optimally treated patients with OSC, the CA125 nadir value is a strong independent prognostic factor. In our study, the CA125 nadir was found to be a strong prognostic factor for PPC. However, unlike many retrospective studies, our study was limited by the small number and heterogeneity of the included patients. Therefore, the significance and utility of the CA125 nadir as a surrogate marker of residual disease after primary treatment for PPC needs to be confirmed in future clinical trials.

Conclusion

Prognosis of the patients with PPC was similar to that of the patients with stage III–IV OSC. The combination of optimal debulking and paclitaxel plus carboplatin chemotherapy may offer the most effective treatment for these patients. The CA125 nadir after cytoreductive surgery can be considered to be a prognostic factor for OS and PFS in patients with PPC.

Table 1. Patient characteristics

Characteristics	PPC (n = 22)	OSC (n = 55)	p
Median age, years (range)	67 (46–75)	58 (45–79)	0.166
Stage, n			
IIIb	1 (4.5%)	2 (3.6%)	
IIIc	17 (77.3%)	36 (65.5%)	0.869
IV	4 (18.2%)	17 (30.9%)	
Performance status, n			
0–1	17 (77.3%)	43 (78.2%)	0.931
2	5 (22.7%)	12 (21.8%)	
Median pretreatment CA125, U/ml (range)	638 (104–12,629)	1,777 (82–71,061)	0.099
Nadir of CA125 concentration, n			
≤26 U/ml	16 (72.7%)	36 (65.5%)	0.945
>26 U/ml	6 (27.3%)	19 (34.5%)	
Median follow-up time, months (range)	29.7 (5.1–93.7)	38.8 (3.9–98.7)	0.062

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Table 2. Patient characteristics

Characteristics	PPC (n = 22)	OSC (n = 55)	p
Timing of debulking surgery, n			
Initial	2 (9.1%)	16 (29.1%)	0.077
Interval	20 (90.9%)	39 (70.9%)	
Residual tumor, n			
≤1 cm (optimal)	12 (54.5%)	28 (50.9%)	0.798
>1 cm (suboptimal)	10 (45.5%)	27 (49.1%)	

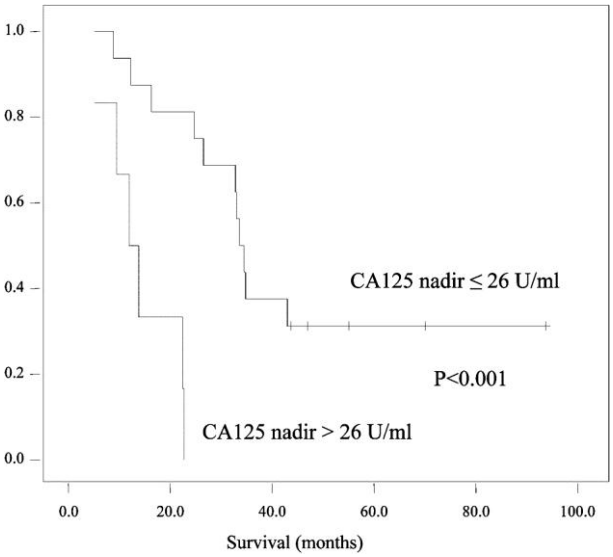

Fig. 1. Overall survival curve on basis of CA125 nadir levels in PPC groups.

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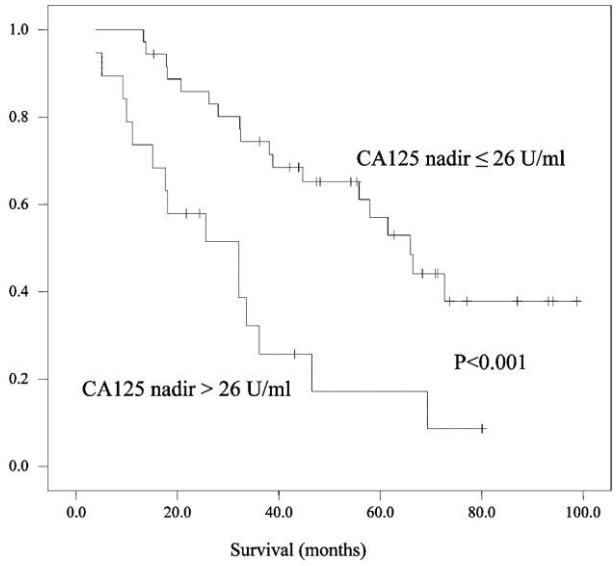

Fig. 2. Overall survival curve on basis of CA125 nadir levels in OSC groups.

References

1 Swerdblow M: Mesothelioma of the pelvic peritoneum resembling papillary cystadenocarcinoma of the ovary: case report. Am J Obstet Gynecol 1959;77:197–200.

2 Truong LD, Maccat ML, Awalt H, Cagle PT, Schwartz MR, Kaplan AL: Serous surface carcinoma of the peritoneum: a clinicopathologic study of 22 cases. Hum Pathol 1990;21:99–110.

3 Eltabbakh GH, Piver MS, Natarajan N, Mettlin CJ: Epidemiologic differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer. Obstet Gynecol 1998;91:254–259.

4 Dalrymple JC, Bannatyne P, Russell P, Solomon HJ, Tattersall MH, Atkinson K, Carter J, Duval P, Elliott P, Friedlander M: Extraovarian peritoneal serous papillary carcinoma. A clinicopathologic study of 31 cases. Cancer 1989;64:110–115.

5 Ayhan A, Taskiran C, Yigit-Celic N, Bozdag G, Gultekin M, Usubutun A, Guler N, Yuce K: Long-term survival after paclitaxel plus platinum-based combination chemotherapy for extraovarian peritoneal serous papillary carcinoma: is it different from that for ovarian serous papillary cancer? Int J Gynecol Cancer 2006;16:484–489.

6 Katsumata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoki D, Tsuda H, Sugiyama T, Kodama S, Kimura E, Ochiai K, Noda K; Japanese Gynecologic Oncology Group: Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009;374:1331–1338.

7 Eltabbakh GH, Werness BA, Piver S, Blumenson LE: Prognostic factors in extraovarian primary peritoneal carcinoma. Gynecol Oncol 1998;71:280–289.

8 Mills SE, Anderson WA, Fechner RE, Austin MB: Serous surfaces papillary carcinoma: a clinicopathologic study of 10 cases and comparison with stage III-IV ovarian serous carcinoma. Am J Surg Pathol 1988;12:827–834.

9 Fromm GL, Gershenson DM, Silva EG: Papillary serous carcinoma of the peritoneum. Obstet Gynecol 1990;75:89–95.

10 Piura B, Meirovitz M, Bartfeld M, Yanai-Inbar I, Cohen Y: Peritoneal papillary serous carcinoma: study of 15 cases and comparison with stage III-IV ovarian papillary serous carcinoma. J Surg Oncol 1998;68:173–178.

11 Meyer T, Rustin GJ: Role of tumour makers in monitoring epithelial ovarian cancer. Br J Cancer 2000;82:1535–1538.

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DOI: 10.1159/000338402

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www.karger.com/cro

12 Juretzka MM, Barakat RR, Chi DS, Iasonos A, Dupont J, Abu-Rustum NR, Poynor EA, Aghajanian C, Spriggs D, Hensley ML, Sabbatini P: CA125 level as a predictor of progression-free survival and overall survival in ovarian cancer patients with surgically defined disease status prior to the initiation of intraperitoneal consolidation therapy. Gynecol Oncol 2007;104:176–180.

13 Prat A, Parera M, Peralta S, Perez-Benavente MA, Garcia A, Gil-Moreno A, Martinez-Palones JM, Roxana I, Baselga J, Del Campo JM: Nadir CA-125 concentration in the normal range as an independent prognostic factor for optimally treated advanced epithelial ovarian cancer. Ann Oncol 2008;19:327–331.

14 Altras MM, Aviram R, Cohen I, Cordoba M, Weiss E, Beyth Y: Primary peritoneal papillary serous adenocarcinoma: clinical and management aspects. Gynecol Oncol 1991;40:230–236.

15 Karlan BY, Baldwin RL, Lopez-Luevanos E, Raffel LJ, Barbuto D, Narod S, Platt LD: Peritoneal serous papillary carcinoma, a phenotypic variant of familial ovarian cancer: implications for ovarian cancer screening. Am J Obstet Gynecol 1999;180:917–928.