Table 5. Reported toxicity in phase III trials comparing IV and IP cisplatin-based chemotherapy (Adopted from NCI Clinical Announcement)

Category	Symptom	Study	IV (%)	IP/IV (%)	*P* value
Auditory					
	Hearing loss (≥grade 2)	Alberts *et al.*[58]	15	5	<0.001
	Tinnitus (≥grade 2)	Alberts *et al.*[58]	14	7	= 0.01
Blood/bone marrow					nr
	Anemia (≥grade 3)	Alberts *et al.*[58]	25	26	ns
		Gadducci *et al.*[53]	8	6	nr
		Kirmani *et al.*[51]	3	7	nr
		Yen *et al.*[55]	12	7	ns
	Granulocytopenia (≥grade 3)	Alberts *et al.*[58]	69	56	= 0.002
	Leukopenia (≥grade 3)	Alberts *et al.*[58]	50	40	= 0.04
		Armstrong *et al.*[57]	64	76	= 0.002
		Gadducci *et al.*[53]	19	24	nr
		Kirmani *et al.*[51]	21	19	nr
		Markman *et al.*[54]	62	77	nr
		Polyzos *et al.*[52]	18	5	<0.01
		Yen *et al.*[55]	21	10	= 0.033
	Thrombocytopenia (≥grade 3)	Alberts *et al.*[58]	9	8	ns
		Armstrong *et al.*[57]	4	12	<0.001
		Gadducci *et al.*[53]	2	0	nr
		Kirmani *et al.*[51]	0	5	nr
		Markman *et al.*[54]	3	49	
		Polyzos *et al.*[52]	10	3	<0.09
		Yen *et al.*[55]	10	7	ns
Constitutional symptoms					
	Fatigue (grade 3–4)	Armstrong *et al.*[57]	4	18	<0.001
		Markman *et al.*[54]	1	3	
	Fever (≥grade 2)	Alberts *et al.*[58]	5	6	ns
		Gadducci *et al.*[53]	9	4	
	Fever (≥grade 3)	Markman *et al.*[54]	1	3	
		Armstrong *et al.*[57]	4	9	= 0.02
Gastrointestinal	≤Grade 3	Markman *et al.*[54]	17	37	
	Emesis (≤grade 3)	Gadducci *et al.*[53]	26	37	
		Armstrong *et al.*[57]	24	46	<0.001
	Nausea/vomiting (grade 2)	Piccart *et al.*[56]	NA	82	
Infection	Grade 1	Piccart *et al.*[56]	NA	26	
	Grades 3–4	Armstrong *et al.*[57]	6	16	= 0.001
		Markman *et al.*[54]	1	4	
Metabolic	≤Grade 3	Markman *et al.*[54]	1	10	
	Hepatic	Armstrong *et al.*[57]	0	3	= 0.05
	Renal	Armstrong *et al.*[57]	1	6	= 0.02
	Creatinine clearance (≤grade 3)	Markman *et al.*[54]	1	5	
	Creatinine clearance (grade 2)	Piccart *et al.*[56]	NA	45	
Neurology					
	Neuromuscular effects at end of treatment (≥grade 2)	Alberts *et al.*[58]	25	15	0.02
	Neurotoxicity (grade 2 or 3)	Piccart *et al.*[56]	NA	15	
	Neurotoxicity (grades 3–4)	Armstrong *et al.*[57]	9	19	<0.001
		Markman *et al.*[54]	9	12	
Pain					
	Abdominal pain (grade 1 or 2)	Piccart *et al.*[56]	NA	38	
	Abdominal pain (≤grade 2)	Alberts *et al.*[58]	2	18	<0.001
	Abdominal pain (grades 3–4)	Armstrong *et al.*[57]	1	11	<0.001

nr, not reported; ns, not significant; NA, not available.

persist at moderate levels among the patients on the IP/IV arm. These findings suggest that the additional toxicity except for paresthesias in the IP delivery is generally transient and not a long-term issue for most patients. Nevertheless, abdominal pain appears to be an unavoidable toxicity because of the nature or IP chemotherapy; the technique to reduce this uncomfortable complication must be explored in the future in

order to make the IP chemotherapy more tolerable and acceptable.

How we reduce the toxicities from IP chemotherapy?

Based on the previous study results, the toxicities related with current cisplatin-based IP chemotherapy would be summarized as (1) IP cisplatin-related toxicities, (2) IP paclitaxel-related toxicities, and (3) catheter-related complications. In the following section, we discuss how we reduce these toxicities.

Reducing IP cisplatin-related toxicities

Easiest way to reduce the IP cisplatin-related toxicities is replacing cisplatin with carboplatin. Fujiwara *et al.* recently published the review article discussing an IP carboplatin-based chemotherapy[63]. Since carboplatin has been shown to be as effective as cisplatin, less toxic (eg, neurotoxicity and renal toxicity)[64,62], and more convenient, carboplatin in combination with paclitaxel became a standard chemotherapy regimen when given intravenously. Since carboplatin is not only less toxic but also easier to administer, it is reasonable to design a trial to test the role of IP carboplatin. However, despite the fact that IV administration of carboplatin has now become a standard platinum agent in the treatment of the epithelial cancer[64,62], IP use of carboplatin has been almost ignored for years.

The reason for this is based on the following two studies: one animal experiment and one retrospective clinical study. In the animal study by Los *et al.* platinum distribution in rat peritoneal tumors after IP treatment with equimolar doses of carboplatin and cisplatin was measured, and no platinum was detected 0.5 mm from the periphery after carboplatin treatment, whereas 14 ppm was detected after cisplatin treatment. They also measured the total platinum concentration in the tumor model after various doses of carboplatin and cisplatin were administered into the IP cavity of mice, and found ten times more carboplatin than cisplatin had to be injected to obtain comparable platinum concentrations in the tumors[65].

Based on this result, Markman *et al.* retrospectively analyzed their clinical data on small number of patients and showed that the response rate was better in cisplatin-based regimen[66], concluding that carboplatin may be inferior to cisplatin when used IP.

The critical issue in these two studies is that these investigators assumed equivalency of dose between carboplatin and cisplatin. For example, in the study of Los *et al.*, the dose of cisplatin and carboplatin administered to the mice was calculated based on weight. The dose of carboplatin that was required to achieve the equivalent tissue platinum concentration that was achieved by administering cisplatin at 5 mg/kg was between 30.0 and 49.2 mg/kg. By comparison, standard IV doses of platinum agents as designed in contemporary clinical trials (such as GOG 158 and Arbeitsgemeinschaft Gynaekologische Onkologie [AGO]) with paclitaxel are cisplatin 75 mg/m^2 and carboplatin AUC of 6–7.5[64,62]. Based on a phase I study by Bookman *et al.*, the dose of carboplatin at AUC of 7.5 was equivalent to 471 mg/m^2 and at AUC of 6 was equivalent to 400 mg/m^2[67]. Therefore, the dose of carboplatin must be at least five to six times more to achieve the equivalent clinical efficacy even when the cisplatin or carboplatin is administered intravenously. In the study of Markman *et al.*, the dose of carboplatin was also too small (200–300 mg/m^2) compared to a considerably high dose of cisplatin (100 mg/m^2). The study also has another limitation because it was a retrospective analysis using a small number of patients. Therefore, an adequate evaluation of IP carboplatin using reasonable dose and sample size is necessary.

As discussed previously in this review article, IP-administered carboplatin is rapidly absorbed into the systemic circulation, and the 24-h platinum AUC in the serum was equivalent regardless of IP or IV administration of carboplatin. On the other hand, 24-h platinum AUC in the peritoneal cavity was approximately 17 times higher when carboplatin was administered with IP route showing that IP infusion of carboplatin is feasible not only as an IP regional therapy but also as more reasonable route for systemic chemotherapy[30].

Clinical efficacy of IP carboplatin-based chemotherapy has shown as a second-line[45,68] or first-line[69] settings. In the second-line study, the response rate was 69–74%. In the study of IP carboplatin-based chemotherapy as a first-line treatment, the authors demonstrated the importance of dose of carboplatin. In this retrospective analysis, the median survival of the patients with small (<2 cm) residual disease was 51 months. Although median survival of patients in this population treated with a dose of carboplatin less than 400 mg/m^2 was 24.5 months, the median survival was not reached until 84 months when greater than or equal to 400 mg/m^2 of carboplatin was given. In the 90 stage III/IV patients, including both small and bulky residual disease, median survival was 25 months with carboplatin dosed less than 400 mg/m^2, whereas it was 51 months with carboplatin dose was greater than or equal to 400 mg/m^2 ($P = 0.0137$).

Toxicity of IP carboplatin plus IV paclitaxel was preliminarily analyzed by Fujiwara *et al.*[70]. They suggested that the recommended dose of IP carboplatin in combination with 3-h IV paclitaxel infusion at 175 mg/m^2 could be AUC of 6.0–7.0. This study led the GOG to conduct a phase I/feasibility study for IP carboplatin to determine the optimal dose with IV paclitaxel for future studies.

Reducing IP paclitaxel-related toxicities

As shown in the GOG 172 trial, there is a possibility that addition of IP paclitaxel on day 8 may have enhanced the survival advantage of patients on the IP arm. On the other hand, it is likely that IP paclitaxel administration caused the severe abdominal pain and prolonged and/or greater neurotoxicity. Substituting paclitaxel with docetaxel seems to be a reasonable solution to reduce neurotoxicity and abdominal pain. As well known by the SCOTROC randomized phase III trial, docetaxel was shown to be significantly less neurotoxic compared with paclitaxel when administered intravenously. A phase I study of IP administration of docetaxel conducted by Morgan *et al.* reported neither toxicity to be dose-limiting toxicities[20]. This should be explored more in the future trials.

Reducing IP catheter-related toxicities

Several studies have reported IP catheter-related complications. Adachi *et al.* reported that catheter complications occur in 27% of patients with temporary IP catheter and in 22% of patients with implantable port[71]. These complications included infection, inflow obstruction, leakage, extrusion, and severe pain, but fortunately, these complications were not serious. With the extensive experience of IP chemotherapy in the Memorial Sloan Kettering Cancer Center, the investigators analyzed catheter-related complications among the patients who were treated in two different time periods. One group was treated between 1985 and 1989[72], and the other was treated between 1989 and 1997[73]. The investigators used a Port-A-Cath system in the earlier period and a multiple fenestrated Bardport system in the later period. Based on their earlier experience, they avoided the catheter placement when bowel surgery was performed in the later period. As a consequence, the complication rate dropped to 9.9% in the later period from 36.8% in the earlier period. The incidence of lower bowel perforation also dropped from 3.5% to 0%. In the latter study, 93% of patients completed treatment.

Walker *et al.* have analyzed the reasons why the prescribed courses of IP chemotherapy on GOG 172 were discontinued[74] and found that catheter complications occurred in 39 of 118 patients (33%). The reasons for IP catheter failure included catheter infection (n = 21), blocked catheter (9), leaking catheter (3), access problems (5), and drainage per vagina (1). In addition, they noted reasons for discontinuing IP therapy potentially related to the presence of a catheter among 4 women with abdominal pain, 4 with bowel complication, and 19 women who refused further IP therapy. They did not find any association between the timing of catheter placement relative to initial surgery or the extent of primary surgery and complication rates. However, IP therapy was not initiated in 16% of patients who did versus 5% of those who did not have a left colon or rectosigmoid colon resection (P = 0.015). This observation also support the observation by Makhija *et al.*, demonstrating that IP catheter complications may be avoided by refraining from IP catheter insertion at the time of bowel resection[73]. In the retrospective analysis by Fujiwara *et al.*,[69] catheter failure occurred less frequently (9.7%), and a median cycle number of IP chemotherapy was 5. In this study, most patients did not undergo bowel resection. This result supports the hypothesis by Walker *et al.*[74] and Makhija *et al.*[73].

As shown in Memorial Sloan Kettering study, catheter materials may also be an important factor. As discussed above, Bardport seems to be more acceptable than Port-A-Cath. There is information that inflow obstruction can be prevented by using an IV port system rather than using IP catheter. The type of catheter and port system should be further explored so as to make the IP chemotherapy more tolerable.

In the mean time, it is preferred to use an IP catheter with port system implantable within the subcutaneous fat tissue (Fig. 13). Preferred timing is at the time of initial laparotomy just before closing the abdomen. Preferred site of port placement is the lower costal margin (Fig. 14). A subcutaneous pocket should be made above the fascia and a subcutaneous tunnel from the catheter entry to the portal pocket should be made. Port should be sutured to the fascia. Heparin (100 units per cc) should be transdermally flushed to determine that flow is not obstructed, and then the incision should be closed.

Future directions

As discussed in this review article, IP cisplatin-based chemotherapy has been shown to have a survival advantage over conventional IV cisplatin-based chemotherapy for patients with optimally resected disease. However, there are a number of unanswered questions that should be resolved before IP

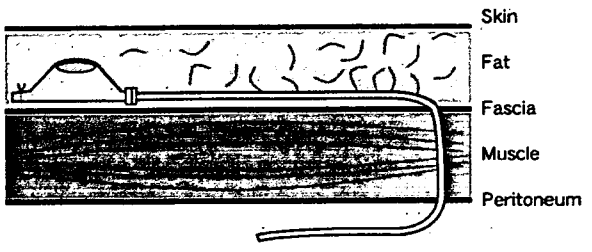

Figure 13. Preferred site for IP port system placement within the subcutaneous fat tissue above fascia.

chemotherapy becomes truly a standard care in the ovarian cancer. To address these questions, gynecological cancer study groups are doing or planning several clinical trials. Following is the list of the questions and efforts to resolve the issue.

(1) Is IP administration of carboplatin replaceable to IP cisplatin as a less toxic alternative?

The GOG is now conducting a phase I trial to determine the optimal dose of IP administration of carboplatin. The Japanese GOG is planning a randomized phase III trial comparing the progression-free survival and overall survival of IP carboplatin plus IV paclitaxel with conventional standard chemotherapy, IV carboplatin plus IV paclitaxel.

(2) Is IP administration of paclitaxel necessary or IP administration of docetaxel acceptable?

GOG is planning a randomized phase I/II trial to determine the role of IP administration of paclitaxel on day 8. In this trial, the feasibility for the administration of both IV paclitaxel and IP cisplatin on day 1 will also be tested as more convenient administration schedule compared to the day 1 IV paclitaxel plus day 2 IP cisplatin schedule of GOG 172 trial. The GOG is also conducting a phase I trial to test the role of IP administration of docetaxel as a less neurotoxic alternative to paclitaxel.

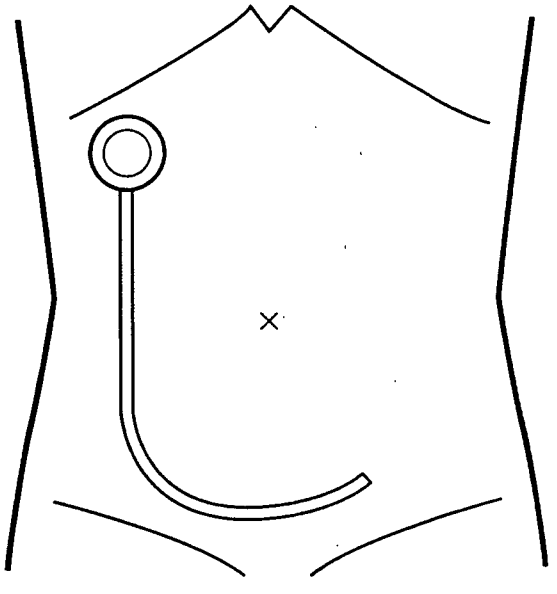

Figure 14. Preferred IP port system placement below the costal margin.

(3) What is the optimal number of IP treatment?

This question is difficult to answer. As summarized in the Table 6, the patients in the IP arm of phase III trials comparing IV versus IP cisplatin-based chemotherapy showed lower completion than patients in the IV arm. The treatment was terminated mainly because of toxicities, but most of the patients who experienced toxicity with IP administration were able to tolerate additional IV chemotherapy. In spite of the fact that a large proportion of the patients was unable to complete the full, planned schedule of IP treatments, intent-to-treat analysis demonstrated a survival benefit. Therefore, it should be important to clarify the true benefit of IP chemotherapy on survival when the IP treatment is completed or the minimum number of IP chemotherapy to maximally improve the survival.

(4) What is the optimal timing for the IP catheter placement and what is the optimal type and material?

These are difficult issues to be solved. In the future GOG IP chemotherapy trials, catheter-related complications will be prospectively assessed in relation to materials, brands, and/or type of openings, single or multiple fenestrations.

(5) Is IP chemotherapy for ovarian cancer with bulky residual tumor as effective as those for small residual tumor?

(6) How effective is IP chemotherapy for retroperitoneal lymph node metastasis?

These two questions are important because the effect of IP chemotherapy in relation to residual tumor theoretically depends on the pharmacokinetics of drugs delivered into the IP cavity. Although the indication

Table 6. Completion rate for prescribed courses of chemotherapy

Study identifier/author/ year of publication	IV regimen (%)	IP/IV regimen for IP administration (%)
SWOG 8501/ GOG 104, Alberts *et al.*, 1996[58]	58	58
GOG 114/ SWOG 9227, Markman *et al.*, 2001[54]	86	71
Gadducci *et al.*, 2000[53]	96	65
EORTC 55875, Piccart *et al.*, 2000[56]	NA	56
GOG 172, Armstrong *et al.*, 2006[57]	90	42

for IP chemotherapy is currently limited to the small residual disease, pharmacologic evidence suggests that the IP platinum chemotherapy could be as effective as or more effective than IV administration[30]. Currently, one of the Japanese gynecological trial groups is conducting the phase II trial to test the efficacy of IP administration of carboplatin in patients with bulky residual tumors and apparent lymph node metastasis.

Conclusions

The IP delivery of anticancer drugs has a great potential to enhance the survival of patients with ovarian cancer. However, further study is necessary before it gains wider acceptance in the gynecological oncology community worldwide.

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Clear Cell Carcinoma of the Ovary

By Toru Sugiyama, MD, PhD, and Keiichi Fujiwara, MD, PhD

Overview: **Clear cell carcinoma of the ovary, which is composed of glycogen-containing clear cells, hobnail cells, and occasionally other cell types, has been recognized since 1971 as a distinct histologic entity according to the World Health Organization classification of epithelial ovarian cancers. Clear cell carcinoma exhibits unique clinical features such as a high incidence of stage I disease, a large pelvic mass, association with thromboembolic complications, and hypercalcemia. Clear cell carcinoma is also frequently associated with endometriosis, and atypical endometriosis is considered a premalignant condition. The incidence of clear cell carcinoma is approximately 5% to 6% throughout the world; however, its incidence in Japan is more than 20%. Clear cell carcinoma has become well known as being resistant to platinum-based chemotherapy. Although it is controversial whether early-stage clear cell carcinoma has an unfavorable prognosis, some of the recent studies demonstrated that the recurrence rate of early clear cell carcinoma is higher than that of other epithelial ovarian cancers and that the survival rate of clear cell carcinoma is similar. In contrast, many studies have indicated that the low response to platinum translates to a significantly shorter survival for advanced clear cell carcinoma. Recent molecular studies support the hypothesis that clear cell carcinoma represents a biologically distinct entity. Further investigation into the molecular biology and genetics of clear cell carcinomas is warranted. Carboplatin/paclitaxel using all subtypes of epithelial ovarian cancers as standard chemotherapy regimen may not be an optimal regimen for clear cell carcinoma because clear cell carcinoma accounts for only 2% to 5% of the cases enrolled in randomized controlled trials. A clear cell carcinoma-specific clinical trial is currently ongoing.**

CLEAR CELL carcinoma of the ovary was originally termed "mesonephroid" by Schiller in 1939 because it was believed to originate from mesonephric structures and resembled renal carcinoma. Clear cell carcinoma is often complicated with endometriosis, whereas hobnail cells bear a very strong morphological resemblance to endometrial Arias-Stella cells; therefore, clear cell carcinoma has been considered to be derived from the Mullerian duct. Since 1973, clear cell carcinoma has been recognized by the World Health Organization classification of ovarian tumors as a distinct histologic entity.[1] Recently, clear cell carcinoma has come to be considered resistant to platinum-based chemotherapy and to have a poorer prognosis with respect to other subtypes of epithelial ovarian cancer. Recent molecular studies support the hypothesis that clear cell carcinoma represents a biologically distinct entity from other epithelial ovarian cancers. However, treatment for clear cell carcinoma has not been scientifically established, thus requiring clear cell carcinoma-specific clinical trials.

PATHOLOGY

Clear cell carcinoma is a malignant ovarian tumor composed of glycogen-containing clear cells and hobnail cells, and occasionally other cell types. Under the supervision of Steven G. Silverberg, MD, a pathology diagnosis guideline for clear cell carcinoma was prepared:

- The tumor invades ovarian stroma, manifested by stromal destruction, desmoplasia, hyalinization, and/or confluence of epithelial elements.
- The tumor growth pattern is tubulocystic, papillary, solid, or a combination of two or all of these.
- The tumor cells contain cytoplasm that is optically clear with hematoxylin staining, or project in a hobnail or peg-like pattern into neoplastic lumens, or display a combination of clear and hobnail patterns. Occasional tumors may be partially or predominantly oncocytic.
- Tumor cell nuclei are pleomorphic, but mitotic figures are rarely numerous.
- Less than 10% of another epithelial carcinoma pattern (endometrioid, serous, and so on) is present. If more than 10%, the diagnosis is mixed-type carcinoma.

CLINICAL BEHAVIOR

Clear cell carcinoma is a histologic subtype of epithelial ovarian cancer showing a different clinical behavior. Clear cell carcinoma frequently presents as a large pelvic mass, rarely occurs bilaterally, and is occasionally associated with hypercalcemia and/or thromboembolic vascular complication.[2-4]

Incidence

The proportion of clear cell carcinoma is higher in the Japanese population (> 20%) than that in the Western countries or other Asian countries (3% to 12%), though the reason for this remains unknown.[2,3,5] Japanese living in the United States exhibit a markedly higher incidence than do whites. These facts indicate the possibility of potentially important ethnic differences.

Relationship with Endometriosis

The results of epidemiologic studies show that approximately half of epithelial ovarian cancers are an adenoma-carcinoma sequence from ovarian cyst and endometriosis, whereas others are de novo in normal ovary and peritoneal epithelial cells. The former is often clear cell carcinoma or endometrioid adenocarcinoma, and the latter is

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Table 1. Distribution by Stage and Histologic Type[6]

Histology	No. of Patients	I (%) a	I (%) b	I (%) c	II (%)	III (%) a	III (%) b	III (%) c	IV (%)
Serous	3,085	5.1	1.1	7.6	7.1	3.4	5.5	53.4	14.7
Mucinous	732	33.9	1.4	21.7	5.7	1.4	4.6	21.6	7.5
Clear cell	494	20.6	1.2	32.2	10.5	1.4	3.8	21.9	6.1

serous adenocarcinoma. It has been reported that endometriosis frequently showed a sequential change to clear cell carcinoma and epithelial ovarian cancer; therefore, atypical endometriosis is considered a precancerous change.[7] Endometriosis causes gene mutation, including loss of heterozygosity (LOH), suggesting that tumor-suppressor-gene inactivation is involved in the development of peritoneal endometriosis.[8] It has also been reported that K-ras mutation is involved in the transformation from endometriosis to clear cell carcinoma,[9] and p53 and phosphatase and tensin homologue deleted on chromosome 10 (PTEN) mutation is often found in epithelial ovarian cancers.[10] The possibility of aggravation of endometriosis is estimated as 2.5% or more. A 9-year follow-up cohort study was carried out in 6,398 patients with endometriotic cyst and 57,165 control patients in Japan, and, respectively, 46 patients (0.72%) and seven patients (0.012%) developed ovarian cancer. The relative risk of aggravation of endometriotic cyst was 12.4 (95% confidence interval [CI], 7.9-17.3). Most ovarian cancers from endometriotic cyst are clear cell carcinoma and epithelial ovarian cancers, and when the incidence in patients in their 20s is considered 1.00, the incidences in patients in their 40s and 50s are 3.60 and 10.7, respectively, indicating that endometriotic cyst can turn cancerous around menopause.[7]

Stage Distribution

Clear cell carcinoma frequently appears during early stages (stage I/II, 59% to 71%), especially stage Ic.[2,3,6,11-13] Approximately 30% of clear cell carcinomas develop into stage III cancer, and rarely have a measurable lesion after the initial surgery. In contrast, serous adenocarcinoma is found not at early stages, but mostly at the advanced stage. Development and proliferation of clear cell carcinoma differ from those of serous adenocarcinoma, as supported by in vitro studies (Table 1).

TREATMENT IMPLICATION

Cytoreductive Surgery

The results of multivariate analysis of clinical studies of clear cell carcinoma patients indicated that residual tumor burden after the initial surgery was an independent prognostic factor. In our retrospective analysis of clear cell carcinoma patients, the complete resection group showed a significantly higher survival rate than did the group with both 1-cm or larger and less than 1-cm residual tumor after the initial surgery.[13] For clear cell carcinoma treatment, maximum cytoreduction effort to achieve no macroscopic disease is most important (Fig. 1).

Resistance to Platinum

Clear cell carcinoma patients rarely have measurable lesions after the initial surgery; therefore, no phase II study with a large number of patients has been conducted. Although, on the basis of small-scale studies, the response rates of platinum-based chemotherapy to clear cell carcinoma were lower (11% to 56%) compared with those of serous adenocarcinoma. The response rates to conventional platinum-based chemotherapy (carboplatin; platinum and cyclophosphamide; and platinum, cyclophosphamide, and doxorubicin) were also poor (11% to 27%).[10,14] The response rates to paclitaxel/platinum chemotherapy, the standard regimen for epithelial ovarian cancer, have been varied, but generally lower (18% to 56%).[14-19] Reporting on a recent preliminary review of the Gynecologic Oncology Group (GOG) experience with clear cell carcinoma in protocols 97, 111, and 132, Birrer noted at the 2003 Annual Meeting of the American Society of Clinical Oncology that the response rate in that review (62% for papillary serous adenocarcinoma and 38% for clear cell carcinoma; p = 0.07) did not reach statistical significance, but that the trend was similar to the previously described findings.[19]

Poorer Survival

Several reports published since 1970 have suggested no differences in survival on the basis of stage between patients with clear cell carcinoma and those with serous adenocarcinoma. In contrast, other recent reports have indicated poorer survival of clear cell carcinoma. Some studies have reported that in its early stages, clear cell carcinoma showed a survival rate similar to those of other

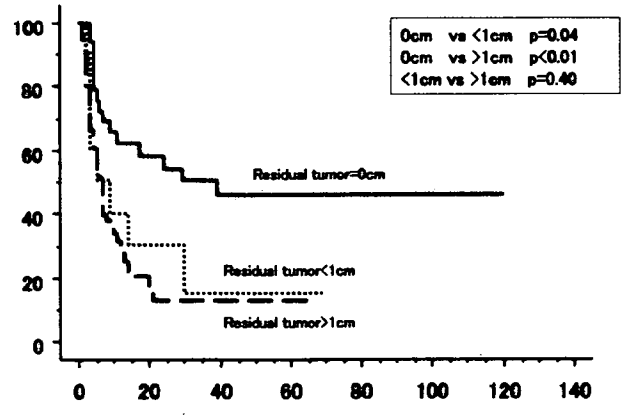

Fig 1. Progression-free survival of patients with stage III and IV disease according to the residual tumor diameter.[12]

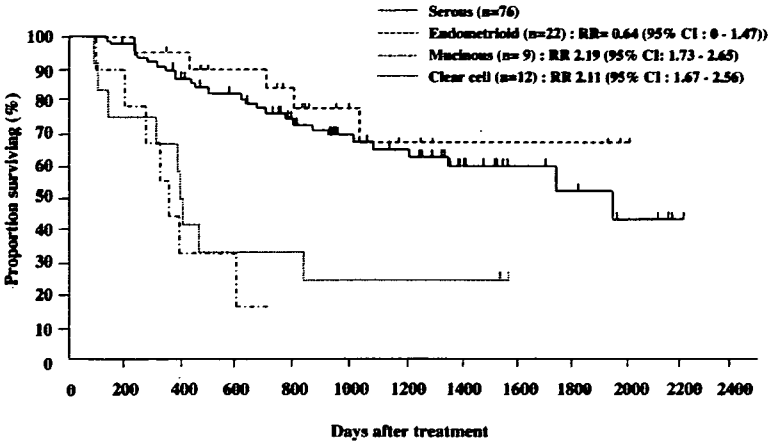

Fig 2. Overall survival.[16] Abbreviation: RR, relative risk of death.

epithelial ovarian cancers, but others showed poor outcomes. Jenison et al and the present authors[3,10] reported that clear cell carcinoma in early stages had a poorer outcome or a tendency toward poor outcome compared with early-stage serous adenocarcinoma. Behbakht et al[20] indicted that stage I clear cell carcinoma had a higher recurrence rate but a similar 5-year survival rate compared with other epithelial ovarian cancers. Kennedy et al[2] reported that the prognosis of stages I/II clear cell carcinoma was similar to that of serous adenocarcinoma, but that of stage IC clear cell carcinoma was poor. The results found that stage IC clear cell carcinoma with malignant ascites showed a significantly poor prognosis among stage I clear cell carcinoma.[12] By summarizing these results, the recurrence rate of clear cell carcinoma in its early stages is higher than that of serous adenocarcinoma, and the survival rate of clear cell carcinoma is similar or poorer. Many studies have reported that clear cell carcinoma in its advanced stages (stages III/IV) showed a lower survival rate than did other epithelial ovarian cancers.[10,11,16,21] Some studies have reported no significant difference between them, although they showed similar trends. Kennedy et al[2] reported that the 5-year survival rate in patients with stages III/IV clear cell carcinoma (17%) was not significantly different from that of other high-grade, stages III/IV epithelial ovarian cancers (22%). Recently, Pectasides et al[15] reported that the median survivals of patients with clear cell carcinoma and serous adenocarcinoma patients were 25 and 49 months, respectively, and the 5-year survival rates were 32% and 39%, respectively, which indicated that clear cell carcinoma had a poorer or similar outcome compared with serous adenocarcinoma. Mizuno et al[11] observed no difference in survival rate between clear cell carcinoma and serous adenocarcinoma in stage III; however, in stages IIIb and IIIc, the 5- and 8-year survival rates of clear cell carcinoma were significantly lower than were those of serous adenocarcinoma. Enomoto et al[16] reported that patients with clear cell carcinoma with more than 1-cm residual tumor had significantly poorer survival than those with serous adenocarcinoma, even though paclitaxel/carboplatin was administered (Fig. 2). A few studies have shown that paclitaxel/platinum chemotherapy was more effective against clear cell carcinoma than was conventional platinum-based chemotherapy before paclitaxel was available; however, its efficacy regarding clear cell carcinoma prognosis remains undetermined.[17-19] Recio et al reported that platinum-based chemotherapy did not appear to improve clear cell carcinoma survival compared with non-platinum based chemotherapy.[4] Irinotecan combined with mitomycin C showed a relatively strong efficacy against clear cell carcinoma as well as irinotecan/platinum chemotherapy.[22] However, these are small-scale studies, and prospective randomized clinical trials are required.

Future

Treatment for clear cell carcinoma has not been yet scientifically established. The efficacy of irinotecan has been reported by basic and clinical studies in Japan. Even though these are relatively large studies for clear cell carcinoma, they are relatively small studies compared with what is normally used in making clinical decisions. An international randomized clinical trial with paclitaxel/carboplatin and irinotecan/cisplatin for clear cell carcinoma is ongoing and the results of this trial are awaited. Other than cytotoxic agents, biologics targeting various molecular targets in the cancer cells would be of the most interest. Among those biologics, those targeting vascular endothelial growth factor appear to be most promising. As demonstrated by a GOG study, bevacizumab is of great interest because it showed improved survival of patients with platinum-resistant/-refractory ovarian cancer compared with the survival of a similar patient population treated by various cytotoxic agents.[23]

Another interesting biologic agent is sunitinib. Sunitnib is a new class of biologic agent targeting certain protein tyrosine kinases, including vascular endothelial growth factor receptor types 1 to 3 and platelet-derived growth factor receptor alpha and beta.[24] Sunitnib has been approved by the U.S. Food and Drug Administration for renal cell carcinoma. Both renal cell carcinoma and clear cell carcinoma of the ovary have been shown to have similar genomic profiles and tyrosine kinase expression. Those agents should be tested in the future regarding

their improvement of the prognosis of clear cell carcinoma of the ovary.

MOLECULAR STUDY

These lower response rates suggest that clear cell carcinoma may have some different molecular biologic aspects from serous adenocarcinoma. For example, recent reports showed that the mutation rate in the *p53* gene was less frequent in clear cell carcinoma than in other histologic subtypes of epithelial ovarian cancer.[25] Kaneuchi et al[26] demonstrated that *WT1* (Wilms tumor 1) sense and antisense promoter were significantly methylated in clear cell carcinoma compared with serous adenocarcinoma. Several authors have reported that multidrug-resistance protein 3 (*MRP3*), which is well known as an adenosine triphosphatase (ATP)-binding cassette transporter, is highly expressed, especially in clear cell carcinoma.[27] Amplification of the human epidermal growth factor receptor type 2 (*HER2/neu*) gene and overexpression of its product is well known to be associated with prognosis in breast cancer. The *HER2/neu* gene has been reported to be highly expressed in clear cell carcinoma among other ovarian histologic subtypes. Schwartz et al[28] reported that glutathione peroxidase 3(*GPx3*), glutaredoxin, and superoxide dismutase (*SOD*) were highly expressed in clear cell carcinoma and suggested that these proteins might render clear cell carcinoma more resistant to chemotherapy. It was recently reported that hepatocyte nuclear factor-1 beta (*HNF-1β*) was a clear cell carcinoma-specific marker and had antiapoptotic effects in clear cell carcinoma cell lines.[29] The ATP-binding cassette, subfamily F, which belongs to the ATP-binding cassette gene superfamily, was highly expressed in patients with clear cell carcinoma who were nonresponsive to chemotherapy, suggesting that *ABCF2* could be a useful marker for the prediction of chemosensitivity.[30] Reed et al[31] demonstrated that mRNA levels of excision repair cross-complementing rodent repair deficiency, complementation group 1, and xeroderma pigmentosum group B complementing tended to be higher in clear cell carcinoma as opposed to other types of epithelial ovarian cancer, and that this may be related to de novo drug resistance against DNA-damaging agents. Itamochi et al[32] revealed the Ki-67 labeling index in clear cell carcinoma was significantly lower than in serous adenocarcinoma, and that the labeling index in responders was significantly higher than that in nonresponders in both clear cell carcinoma and serous adenocarcinoma, and concluded that low-proliferation activity may contribute to chemoresistance in clear cell carcinoma. Suppression of clear cell carcinoma-specific molecular markers related with chemoresistance may represent a useful strategy for the treatment of clear cell carcinoma.

CONCLUSION

In the initial surgery, the tumor should be resected to as great an extent as possible. The goal is complete resection (no visible disease).

In chemotherapy, drugs without cross-resistance to platinum and molecular-targeted drugs should be introduced. Clear cell carcinoma should be studied in separate trials. At present, a study of Gynaecologic Cancer Intergroup/Japanese Gynecologic Oncology Group3017 is in progress and will be completed as soon as possible with international collaborations. Recurrent cancer requires treatment using molecularly targeted drugs based on molecular biology.

Clear cell carcinoma has a markedly different molecular biology from other epithelial ovarian cancers, and thus should be studied on the basis of molecular biology. Cross-organ treatment for cancer based on molecular characteristics is expected.

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Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging

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A retrospective analysis was performed to evaluate the clinical characteristics and prognostic factors in the patients with clear cell carcinoma (CCC) of the ovary. After central pathological review and scanning of the medical records of nine Japanese institutions between 1992 and 2003, a total of 254 patients with CCC of the ovary were enrolled in the present study. Mean age was 52.4 years (range 23–73 years). Tumours were 13% (33/254) stage Ia, 36% (92/254) stage Ic, 13% (33/254) stage II, 30% (80/254) stage III, and 6% (16/254) stage IV. Five-year progression-free survival and overall survival was 84 and 88% in stage I, 57 and 70% in stage II, 25 and 33% in stage III and 0 and 0% in stage IV, respectively. Retroperitoneal lymph node metastasis was observed in 9% in pT1a tumours, 7% in pT1c tumours, 13% in pT2 tumours, and 58% in pT3 tumours, respectively. There was no survival benefit according to chemotherapeutic differences in the patients who received complete surgical staging procedures and conventional chemotherapy. Peritoneal cytological status was an independent prognostic factor in stage Ic patients ($P = 0.03$) and only residual tumour diameter was an independent prognostic factor in stage III, IV patients ($P = 0.02$). Our results suggest that cytoreductive surgery resulting in no residual tumour only could improve the prognosis of advanced CCC patients.
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Cancer of the ovary has the worst prognosis of all gynaecological malignancies in the United States (Edwards *et al*, 2005) and Europe (Bray *et al*, 2005). Survival rate of patients with ovarian cancer has dramatically improved after introduction of platinum-based chemotherapy, but there still exist a large number of patients showing no response to the treatments. Although response to anticancer drugs is not easy to predict, *in vitro* studies suggested that acquired resistance to cisplatin has been associated with increased levels of glutathione and glutathione-S-transferase activity, increased metallothionein and decreased accumulation of cisplatin (Kikuchi *et al*, 1998). Histological subtypes such as clear cell carcinoma (CCC) and mucinous adenocarcinoma had been suggested as one of the most reliable criteria predicting the ineffectiveness of chemotherapy.

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Clear cell carcinoma (CCC) was initially termed as mesonerhroid in 1939 (Schiller, 1939), and since 1973 it was strictly defined by World Health Organization as lesions characterised by clear cells growing in solid/tubular or glandular patterns as well as hobnail cells (Serov *et al*, 1973). Since then, many literatures have identified the distinctive behaviour of the tumors as compared with other histological subtypes of ovarian neoplasms. The most distinctive difference is that patients with CCC of the ovary have lower response rate to anticancer drugs. To our knowledge, only a few clinical studies have evaluated the response rates for CCC patients with measurable disease. The response rate of chemotherapy for CCC was 11.1% with platinum-based regimens (Sugiyama *et al*, 2000) and 22–56% with paclitaxel plus carboplatin. (Enomoto *et al*, 2003; Ho *et al*, 2004).

Another factor that might contribute to prognosis of ovarian cancer is the degree of cytoreductive surgery including lymphadenectomy. Complete surgical staging including para-aortic lymphadenectomy might influence the prognosis in early-stage CCC cases (Ho *et al*, 2003). Furthermore, the patients with pure-type CCC had worse overall survival than those with mixed-type CCC (Ho *et al*, 2004).

To evaluate the clinical characteristics of the patients with CCC of the ovary and to determine the impact of surgery and

chemotherapy on prognosis of those patients, we conducted a retrospective study over 11-year period of a sample of 254 patients diagnosed with pure-type CCC in the departments of nine Japanese institutions.

MATERIALS AND METHODS

Patients and tumours

Between 1992 and 2002, 254 patients with CCC of the ovary were identified by scanning the medical records of the collaborating institutions and central pathological review. Patients received initial treatment and follow-up at nine institutions belonging to Japan Clear Cell Carcinoma Study Group; National Defence Medical College Hospital, Tohoku University Hospital, Aichi Cancer Center Hospital, Osaka Medical College Hospital, Osaka City General Hospital, Jichi Medical College Hospital, Tottori University Hospital, Kobe National Hospital, Iwate Medical College Hospital.

Initially, 337 patients were accrued from medical records of each institution. All pathological specimens from primary surgery were reviewed under central pathological review by two independent pathologists with no knowledge of patients' clinical data. Tumours were diagnosed as CCC if typical clear or hobnail cells growing in a papillary, solid, or tubulocystic pattern appeared in >90% of all pathological specimens. After pathological review, three cases were excluded; two diagnosed as mixed epithelial ovarian cancers and the other diagnosed as CCC derived from mature cystic teratoma, and 334 cases were identified as the patients with pure-type CCC of ovary. In those patients, 80 patients were excluded owing to insufficient surgery lacking complete surgical staging procedures: 13 cases in pT1a tumours, 51 cases in pT1c tumours, 16 cases in pT2 tumours, respectively. The rest 254 patients were enrolled on the present study. Patients of FIGO stage Ic were classified into three subtypes according to pathological characteristics; Ic (capsule ruptured) for the patients with ruptured capsule at laparotomy, Ic (ovarian surface) for those with tumour on ovarian surface, and Ic (ascites/malignant washing) for those with positive malignant cells in the ascites or positive peritoneal washing.

All 254 patients underwent complete surgical staging procedures including hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, omentectomy, pelvic lymphadenectomy and paraaortic lymphadenenctomy. Staging was based on the FIGO classification. The resected lymph node counts were not considered for the completion of the lymphadenectomy. A pN1 case was determined as having one or more lymph node metastasis in pelvic or paraaortic lymph nodes.

Chemotherapy

Two hundred and forty-two (95.3%) patients received postoperative chemotherapy after initial surgery. Second look operation or second reductive surgery was done by surgeon's preference. Combination therapy of cyclophosphamide and doxorubicin and cisplatin (CAP) was as follows: one cycle consisted of a drip infusion of 50–75 mg m^{-2} cisplatin for 3 h accompanied by an i.v. injection of 50 mg m^{-2} doxorubicin and 500 mg m^{-2} cyclophosphamide and six cycles were given every 4 weeks. Paclitaxel and platinum regimen consisted of an infusion of 175–180 mg m^{-2} of paclitaxel and 50–75 mg m^{-2} of cisplatin or carboplatin (AUC = 5–6). Other regimens included the combination chemotherapy irinotecan hydrochloride and cisplatin (40 cases) and irinotecan hydrochloride and mitomycin C (20 cases) and irinotecan hydrochloride and etoposide (3 cases). One cycle of irinotecan hydrochloride and platinum regimen consisted of a drip infusion of 50–60 mg m^{-2} of cisplatin on day 1 and 50–60 mg m^{-2} of CPT-11 on day 1, 8, 15 and 1 week off and it was repeated every 4 weeks.

Response was evaluated with CT or MR images for patients with measurable disease. 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 >50% decrease in tumour 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 >25% increase in tumour size. Serum levels of tumour markers including CA125 were not used for response evaluation of chemotherapy in the present study.

The time to progression was defined as the interval from the date of primary surgery until the date of recurrence or tumour progression (PD). 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

Kaplan–Meier method was used for calculation of patient survival distribution. The significance of the survival distribution in each group was tested by a generalized Wilcoxon test and the log-rank test. The χ^2-test and Student's t-test for unpaired data were used for statistical analysis. A P-value of <0.05 was considered statistically significant. The Stat View software ver.5.0 (SAS Institution Inc., Cary, NC, USA) was used to analyse the data.

RESULTS

Patients and tumours

The characteristics of the study population are summarized in Table 1. Mean age was 52.4 years (range 23–73 years). Tumours were 13% (33/254) stage Ia, 36% (92/254) stage Ic, 13% (33/254) stage II, 31% (80/254) stage III, and 6% (16/254) stage IV, respectively. There is no case with stage Ib tumours. Among 92 cases of stage Ic, there were 45 cases (49%) of Ic (capsule

Table 1 Characteristics of the patients

Characteristics	No. of patients (%)
All cases	254
Age (years)	
<55	147 (57.9)
>55	107 (42.1)
FIGO Stage	
Ia	33 (13.0)
Ic (ovarian surface)	3 (1.2)
Ic (capsule ruptured)	45 (17.7)
Ic (ascites/malignant washing)	44 (17.3)
II	33 (13.0)
IIIa,b	5 (2.0)
IIIc	75 (29.5)
IV	16 (6.3)
Residual tumour diameter	
0 cm	176 (69.3)
<1 cm	18 (7.1)
>1 cm	60 (23.6)
Postoperative chemotherapy	
CAP[a]	76 (29.9)
Paclitaxel+platinum	103 (40.6)
Others	63 (24.8)
None	12 (4.7)

[a]CAP, cyclophosphamide+doxorubicin+cisplatin.

ruptured), 3 cases (3%) of Ic (ovarian surface) and 44 cases (48%) of Ic (ascites/malignant washing), respectively. In 75 stage IIIc tumours, 15 cases (20%) were upstaged to stage IIIc because of retroperitoneal lymph node metastasis and 20 patients (27%) had both retroperitoneal lymph node metastasis and intra-peritoneal disease. Residual tumour diameter after primary debulking surgery was 0 cm in 176 cases (69%), less than 1 cm in 18 cases (7%), and more than 1 cm in 60 cases (24%), respectively.

Postoperative chemotherapy was offered for all patients, and 242 patients (95%) received anticancer drugs. Eight patients in stage Ia and four patients with stage Ic (capsule ruptured) refused postoperative chemotherapy.

Precise lymph node status according to pT distribution was documented in Table 2. Lymph node metastasis was documented in 3 of 36 patients (9%) in pT1a tumours, 7.1% in pT1c tumours, 13% in pT2, and 58% in pT3 tumours, respectively. Retroperitoneal lymph node metastasis in pT3 tumours was observed significantly more frequent than in pT1, 2 tumours (58.0 *vs* 8.7%, $P<0.001$, χ^2-test).

Response of chemotherapy

Response judged with CT or MRI images was assessable in 73 cases (29%) in 242 patients who received postoperative chemotherapy. Only 5 of 30 cases (16%) responded to CAP regimen. Progressive disease was documented in 23 patients (77%) and SD was observed in 2 patients (7%). In 28 patients treated with paclitaxel and platinum, response was observed in nine cases (32%) including one case with CR. In the patients treated with other regimens, response was observed in 3 of 10 patients (30%) treated with irinotecan hydrochloride and cisplatin. There is no responder in seven assessable patients who received combination with irinotecan hydrochloride and mitomycin C.

The median duration of progression-free survival for the patients with measurable disease was 4 months (range, 1–20 months) in CAP regimen, 5 months (range, 1–21 months) in paclitaxel and platinum, and 3 months (range, 2–20 months) in irinotecan hydrochloride and cisplatin, respectively.

Table 2 Rates of lymph node metastasis according to pT status

pT status	pN1	pN0	Rate of Lymph Node metastasis (%)
pT1a ($n=36$)	3	33	9.1
pT1c ($n=99$)	7	92	7.1
pT2 ($n=38$)	5	33	13.1
pT3 ($n=81$)	47	34	58.0
Total ($n=254$)	62	192	24.4

Clinical course

Average follow-up for all CCC patients in the present study is 47.4 months. Five-year progression-free survival and overall survival was 84 and 88% in stage I, 57 and 70% in stage II, 25 and 33% in stage III and 0 and 0% in stage IV, respectively (Figure 1). Although there is no statistically significant difference in progression-free survival between patients with stage Ic (capsule ruptured) and those with stage Ia ($P=0.11$), progression-free survival of the patients with stage Ic (ascites/malignant washing) and Ic (ovarian surface) was significantly worse than that of stage Ic (capsule ruptured) ($P=0.04$)(Figure 2). Multiple regression survival analysis for stage Ic patients with CCC revealed that positive peritoneal cytology was the only independent prognostic factor ($P=0.03$; Relative risk, 3.40; 95% CI, 1.14–10.18). Cumulative progression-free survival of pT1M0 patients with positive node was significantly lower than those with negative node ($P<0.01$). Five-year progression-free survival was 84% in pT1N0 patients and 56% in pT1N1 patients, respectively.

Progression-free survival curves of stage III, IV patients according to the residual tumour diameter were shown in Figure 3. Median progression-free survival duration was 39 months in the

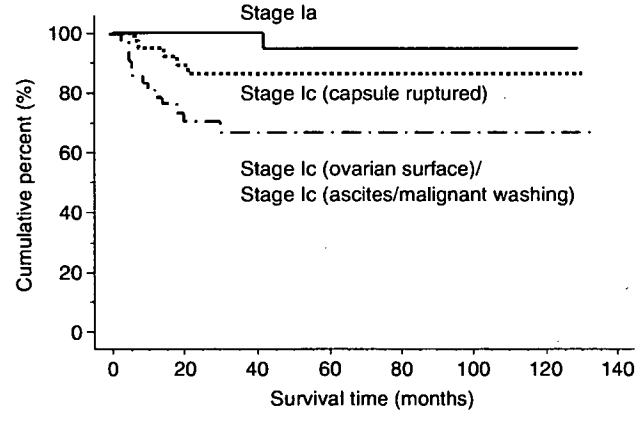

Figure 2 Progression-free survival of patients with FIGO stage I patients. There is no significant difference between patients with stage Ic (capsule ruptured) and those with stage Ia ($P=0.11$). Survival of the patients with stage Ic (ascites/malignant washing) and Ic (ovarian surface) was significantly worse than that of stage Ic (capsule ruptured) ($P=0.04$).

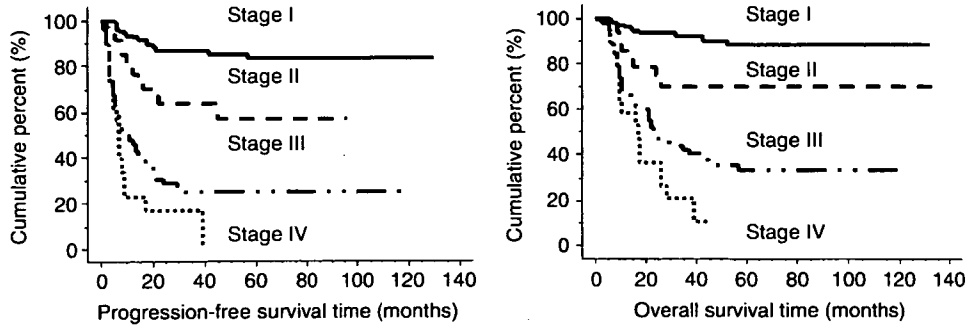

Figure 1 Progression-free survival and overall survival of patients depending on their FIGO stage. Five-year progression-free survival and overall survival was 84 and 88% in stage I, 57 and 70% in stage II, 25 and 33% in stage III and 0 and 0% in stage IV, respectively. *P*-values in progression-free survival were as follows: Stage I *vs* stage II, $P<0.01$; stage II *vs* stage III, $P<0.01$; stage III *vs* stage IV, $P=0.35$. *P*-values in overall survival were as follows: Stage I *vs* stage II, $P<0.01$; stage II *vs* stage III, $P<0.01$; stage III *vs* stage IV, $P=0.17$.

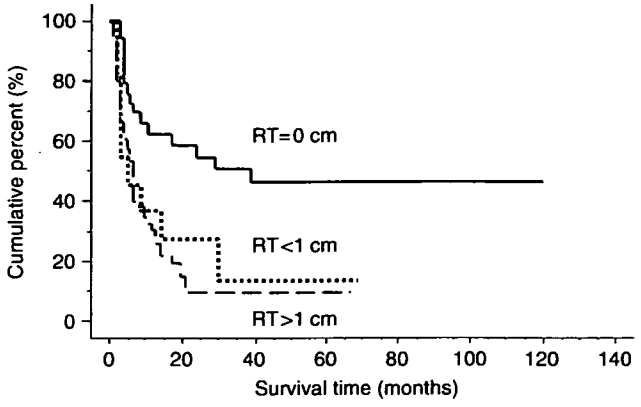

Figure 3 Progression-free survival of stage III, IV patients according to the residual tumour (RT) diameter. There is no significant prognostic difference between the patients with the tumour diameter less than 1 cm and those with the tumour diameter more than 1 cm ($P=0.40$). The patients with no residual tumour had significantly better progression-free survival than those with the tumour less than 1 cm ($P=0.04$) or those with tumour diameter more than 1 cm ($P<0.01$), respectively. Median progression-free survival duration was 39 months in the patients with no residual tumour, 7 months in those with the tumour diameter less than 1 cm, and 5 months in those with residual tumour diameter more than 1 cm, respectively.

Table 3 Multiple regression survival analysis for stage III, IV patients with CCC

Variables	Hazard ratio	95% confidence interval	P
Age (years)			0.96
<54	1		
>55	0.99	0.60; 1.61	
PS			0.67
0	1		
1,2	1.06	0.79; 1.43	
FIGO stage			0.22
III	1		
IV	1.47	0.80; 2.70	
Residual tumour			0.02
None	1		
< 1 cm	2.23	0.89; 5.54	
> 1 cm	3.17	1.68; 6.00	
Chemotherapy			0.24
CAP[a]	1		
Paclitaxel+platinum	0.56	0.48; 1.88	
Others	0.95	0.32; 1.22	

[a]CAP, cyclophosphamide+doxorubicin+cisplatin.

patients with no residual tumour, 7 months in those with the tumor diameter less than 1 cm, and 5 months in those with residual tumour diameter more than 1 cm, respectively. There is no significant prognostic difference between the patients with the tumour diameter less than 1 cm and those with the tumour diameter more than 1 cm ($P=0.40$). The patients with no residual tumour had significantly better progression-free survival than those with the tumour less than 1 cm ($P=0.04$) or those with tumour diameter more than 1 cm ($P<0.01$), respectively.

Multiple regression analysis in stage III and IV patients revealed that chemotherapeutic regimen was not an independent prognostic factor ($P=0.24$) and only residual tumour diameter was an independent prognostic factor in stage III and IV patients ($P=0.02$) (Table 3).

DISCUSSION

The present study and previous studies support that CCC of the ovary tended to present at earlier stages. Proportion of stage I/II tumours ranged from 59 to 71% (Yoonessi *et al*, 1984; Crozier *et al*, 1989; Jenison *et al*, 1989; Kennedy *et al*, 1989; O'Brien *et al*, 1993; Behbakht *et al*, 1998; Sugiyama *et al*, 2000). One of the reasons for the early detection was explained by the slow growing tumour behaviour (Itamochi *et al*, 2002a) and frequent presentation of the tumours as relatively large pelvic masses (Kennedy *et al*, 1989; Behbakht *et al*, 1998). In the present study, the status of peritoneal cytology was identified as an independent prognostic factor in FIGO stage Ic patients. Although tumour progression was observed in 5 (11%) of 45 stage Ic (capsule ruptured) tumours and one (3%) of 33 stage Ia tumours, there is no significant survival difference between two groups. Recent report analysing prognosis of early-staged ovarian cancer including only 25 CCC cases (26.6%) in 94 carcinomas showed no statistical significant difference between stages Ic preoperative *vs* intraoperative rupture (Leitao *et al*, 2004). Another report including higher ratio of CCC patients identified that stage Ic (capsule ruptured) patients showed significantly poorer survival than stage Ia patients (Mizuno *et al*, 2003). The present study implied the importance to remove the tumour mass without intraoperative rupture, especially in CCC patients.

Even in stage I ovarian cancer including all histological subtypes, the incidence of positive lymph nodes was not low, ranging from 5.1 to 20% (Sakuragi *et al*, 2000; Cass *et al*, 2001; Morice *et al*, 2003). It was reported that serous tumour had a higher incidence of lymph node involvement than non-serous tumors (Takeshima *et al*, 2005). Although the true incidence of lymph node metastasis in CCC tumour had not been clear, the present study revealed the frequency of metastasis in a large number of the CCC patients. Lymph node metastasis was observed in 3 of 36 patients (9.1%) in pT1a tumours, 7.1% in pT1c tumours, 10.8% in pT2 tumours, respectively. Fifteen (8.7%) of 173 patients who had pT1 or pT2 tumors were upstaged as stage IIIc tumours based on lymph node status. In general, prognostic significance of retroperitoneal lymph node metastasis in early-staged ovarian cancer patients was controversial. Survival rates with node-positive disease were significantly lower in clinical stage I and II disease (Kanazawa *et al*, 1999; Sakuragi *et al*, 2000; Negishi *et al*, 2004). In contrast, another report showed that the prognoses for clinical stage I/II patients with or without lymph node metastasis were similar (Onda *et al*, 1998). In pT1 CCC patients of the present study, lymph node status was identified as a strong prognostic factor and it is essential to accurately evaluate the lymph node status through complete surgical staging procedures. The study, called Adjuvant ChemoTherapy in Ovarian Neolasm (ACTION), revealed that no benefit of adjuvant chemotherapy was observed in early-stage ovarian cancer with optimal surgical procedures (Trimbos *et al*, 2003). In the present study, 12 patients with stage Ia or stage Ic (capsule ruptured) refused to receive chemotherapy, but there was no evidence of recurrence in median follow-up period of 44 months (range: 6–63 months), which might support the results of ACTION study.

Previous Japanese report have shown that the chemotherapeutic effect was assessable in only 27 patients (26.7%) in 101 CCC cases, in contrast it was assessable in 47% of serous adenocarcinoma (Sugiyama *et al*, 2000). In our series of CCC patients, patients with residual tumour diameter more than 1 cm were documented in only 60 (18%) of 254 cases, and the chemotherapeutic effect was assessable in only in 73 cases (29%) in 242 patients who received adjuvant chemotherapy. As the residual tumour after debulking surgery often lacked measurable tumour diameter to evaluate the

effects of adjuvant chemotherapy in CCC patients, it has been quite difficult to select superior regimen.

There have been only a few reports to document the response of anticancer agents for CCC patients, but each of them included relatively small number of cases. The present study confirmed that CAP regimen showed a low response rate and quite a high incidence of PD in CCC patients as described previously (Sugiyama *et al*, 2000). The combination chemotherapy consisting of paclitaxel and platinum has been established as standard therapy for ovarian cancer. One report of paclitaxel and platinum regimen for CCC patients revealed that the response was observed in two of nine cases (22%) (Enomoto *et al*, 2003), and the other report of paclitaxel plus platinum chemotherapy showed the response was observed in 9 of 15 cases (56%) (Ho *et al*, 2004). These two studies including the present study suggested that paclitaxel plus platinum regimen had higher response rate compared to platinum-based chemotherapy. One report showed survival benefit of conventional chemotherapy with paclitaxel and platinum after complete surgery in CCC patients (Ho *et al*, 2003). However, the results from our series of CCC patients showed that there was no survival benefit with chemotherapy with paclitaxel and platinum compared with CAP regimen in both early and advanced cases. Irinotecan hydrochloride was preliminary introduced for CCC patients in clinical settings (Shimizu *et al*, 1998; Adachi *et al*, 1999; Kita *et al*, 2000), but there is no large 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.

Recent studies have suggested that CCC tumour showed a distinctive molecular behaviour from other histological subtypes. *In vitro* study suggested that paclitaxel and irinotecan hydrochloride were the candidates for anti-neoplastic agents for CCC (Itamochi *et al*, 2002b), but the present study has failed to prove the survival benefit of these two drugs in CCC patients. Another strategy for CCC tumours might be the additive use of molecular targeting agents. It was reported that hepatocyte nuclear factor-1 beta (HNF-1 β) was a CCC-specific marker and had anti-apoptotic effects in CCC cell lines (Tsuchiya *et al*, 2003). Another candidate marker could be ABCF2, which belongs to the ATP-binding cassette gene superfamily and is highly expressed in CCC and non-responders for chemotherapy (Tsuda *et al*, 2005). Suppression of CCC-specific molecular markers such as HNF-1 β or ABF2 may be another strategy for the treatment of CCC of the ovary. The present study clarified the significant prognostic importance of positive peritoneal cytology in early-stage CCC disease, and no macroscopic residual tumour in advanced CCC tumours, respectively. However, there was a little impact of chemotherapeutic effects on both early and advanced diseases. Although further studies are needed to identify effective agents in both anti-neoplastic agents and molecular targeting agents, our study provides the fundamental characteristics of CCC of the ovary.

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PROTOCOL GOG-0218

A PHASE III TRIAL OF CARBOPLATIN AND PACLITAXEL PLUS PLACEBO VERSUS CARBOPLATIN AND PACLITAXEL PLUS CONCURRENT BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY PLACEBO, VERSUS CARBOPLATIN AND PACLITAXEL PLUS CONCURRENT AND EXTENDED BEVACIZUMAB, IN WOMEN WITH NEWLY DIAGNOSED, PREVIOUSLY UNTREATED, STAGE III OR IV, EPITHELIAL OVARIAN OR PRIMARY PERITONEAL CANCER NCI-SUPPLIED AGENT(S):

BEVACIZUMAB/ PLACEBO (NSC #704865, IND #7921) **(06/26/06) (08/06/07)**

NCI Version Date: 07/13/07

Includes: Revisions 1-3

POINTS:
PER CAPITA –30
MEMBERSHIP - 6

TRANSLATIONAL RESEARCH PER CAPITA–Award based on specimen submissions. Distribution: Frozen tumor-3 points, tumor block-2 points (2nd choice tumor sections and scroll-1 point), frozen serum-0.5 point and frozen plasma-0.5 point.**(06/26/06)**

TRANSLATIONAL RESEARCH MEMBERSHIP - Bonus membership point will be awarded for submission of satisfactory frozen tumor, tumor block, frozen serum and frozen plasma. **(06/26/06)**

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OPEN TO PATIENT ENTRY SEPTEMBER 26, 2005 REVISED JANUARY 16, 2006 REVISED JUNE 26, 2006 REVISED AUGUST 6, 2007

医療機関の長および治験責任医師は、本治験実施計画書を遵守することに合意する。

200　年　　月　　日

医療機関名：

医療機関長名：　　印

200　年　　月　　日

治験責任医師名：　　印

This study is supported by the NCI Cancer Trials Support Unit (CTSU). **(08/06/07)**

Institutions not aligned with GOG 0218 will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://members.ctsu.org
- Send completed site registration documents to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- Patient enrollments will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the GOG. Case report forms (with the exception of patient enrollment forms), clinical reports, and transmittals must be sent to GOG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- Data query and delinquency reports will be sent directly to the enrolling site by GOG via GOG's web based system. Please send query responses and delinquent data to GOG as directed and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the GOG Statistical and Data center.

Patient enrollments from institutions that are not aligned with GOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to CTSU Data Operations unless otherwise specified in the CTSU logistical appendix. CTSU will use the GOG-0218 number as required for reporting to GOG and NCI and when registering patients through the GOG Registrar. CTSU participants and institutions will be instructed to use the GOG-0218 study number on all data forms.

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION (XX/XX/07)

To submit site registration documents:	For patient enrollments:	Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 8:00 AM – 8:00 PM Eastern Time, Monday Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	GOGO Statistical and Data Center at Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263-0001 Phone: 716-845-5702 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

For patient eligibility or treatment-related questions contact the Study Chair of the Coordinating group.
For questions unrelated to patient eligibility, treatment or data submission contact the CTSU Help Desk by phone or email:
All other questions (including forms-specific questions) should be communicated by phone or e-mail to:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
The CTSU Public Web site is located at: www.ctsu.org
The CTSU Registered Member Web site is located at http://members.ctsu.org

CTSU logistical information is located in Appendix VIII.. (08/06/07)

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