Original Articles

Second-line chemotherapy for carboplatin/paclitaxel-refractory ovarian cancer: are multi-agent chemotherapies of little value truly?

T. Ota, N. Takeshima, K. Takizawa

Department of Gynecology, Cancer Institute Hospital, Tokyo (Japan)

Summary

Purpose: We examined whether second-line multi-agent chemotherapies are of any value for carboplatin/paclitaxel (TC)-refractory ovarian cancer. *Methods:* Subjects included 60 patients with ovarian, peritoneal, or tubal carcinoma who received second-line platinum-based combination chemotherapy. Thirty-nine were treated with irinotecan/cisplatin or nedaplatin and 21 with docetaxel/cisplatin shortly after TC failure. Patients were divided between those who were refractory to initial platinum-based chemotherapy (n = 29, Group A) and those who were platinum-sensitive (n = 31, Group B). Efficacy and safety of the combination chemotherapies were compared between the two groups. *Results:* Response to the combination chemotherapy was 10.3% in Group A and 41.9% in Group B. Median time to disease progression was 4.02 months and 7.21 months, respectively *(p = 0.006)*, and median survival time was 7.89 months and 9.23 months, respectively *(p = 0.003)*. There was no difference in response between the two regimens. Grade 3-4 hematologic toxicities were more frequent with the docetaxel regimen. *Conclusion:* The choice between agents for second-line chemotherapy for TC-refractory ovarian cancer should be based on whether the cancer was previously platinum-sensitive. With a history of such response, multi-agent chemotherapies are worth considering after TC failure. With no previous response, the expected efficacy of second-line multi-agent chemotherapy is low, suggesting the use of monochemotherapy.

Key words: Second line; Combined chemotherapy.

Introduction

Today, standard first-line chemotherapy for treatment of ovarian carcinoma involves both paclitaxel and platinum [1-4]. Long-term survival for women with advanced-stage ovarian carcinoma is only 30%, even among those who have had optimal cytoreduction and front-line combination chemotherapy [1, 3, 5, 6]. Several reports have suggested that patients with ovarian cancer who initially respond to platinum-based treatment and in whom the disease recurs may respond to retreatment with platinum-based agents. Patients with recurrent ovarian carcinoma are considered to fall into one of two groups for which the prognoses differ. Patients in whom the disease progresses during primary therapy or after a treatment-free interval of < 6 months are considered platinum-refractory; those in whom the disease relapses or the disease progresses after a treatment-free interval of > 6 months are considered platinum-sensitive. Platinum-sensitive patients are more likely to respond to subsequent chemotherapy; the probability of a second response increases up to 60% [7-12], and as a result, the prognosis is more favorable [9, 11, 13-15]. In addition, several studies have shown that the response rate improves with longer platinum-free periods, thus providing evidence that nonplatinum-based compounds may be efficacious in a subgroup of platinum-sensitive patients [9, 16-18].

Platinum-sensitive patients receiving platinum-based combination chemotherapy vs single-agent chemotherapy also show prolonged survival and progression-free survival intervals [19-21], but platinum-based combination regimens are not always successful as second-line treatment in platinum-sensitive patients. In such cases, single-agent chemotherapy may be appropriate.

We conducted a study to examine the efficacy and safety of second-line chemotherapy in patients with ovarian cancer, asking whether multi-agent chemotherapies are always useless in patients for whom first-line carboplatin/paclitaxel (TC) chemotherapy has failed.

Patients and Methods

Subjects of our study included 60 patients with ovarian, peritoneal, or tubal carcinoma who were treated by second-line platinum-based combination chemotherapy at the Cancer Institute Hospital, Tokyo, Japan, between June 2005 and December 2008. All patients had received a combination of platinum and taxane combined chemotherapy as first-line chemotherapy. Disease stages were determined according to the International Federation of Gynecology and Obstetrics criteria.

Thirty-nine of the 60 patients were treated with irinotecan (CPT-11) plus cisplatin (CDDP) or nedaplatin (NDP), and 21were treated with docetaxel (DTX) plus cisplatin (DP). The patients were divided into two groups: those in whom the disease progressed during the initial platinum-based chemotherapy, in whom the disease remained stable, or in whom the disease relapsed within six months after completion of the platinum-based chemotherapy (platinum-refractory group, Group A; n = 29) and those in whom a progression-free interval of > 6 months was seen after completion of the platinum-based chemotherapy (platinum-sensitive group, Group B; n = 31). The two patient groups are shown in Figure 1.

Revised manuscript accepted for publication December 16, 2010

Fig. 1

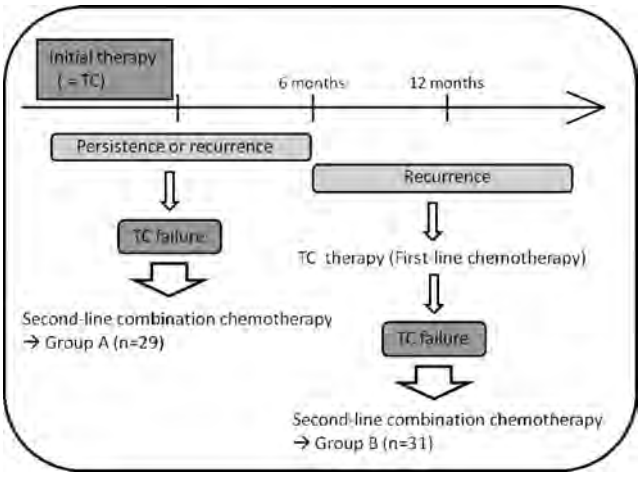

Fig. 2

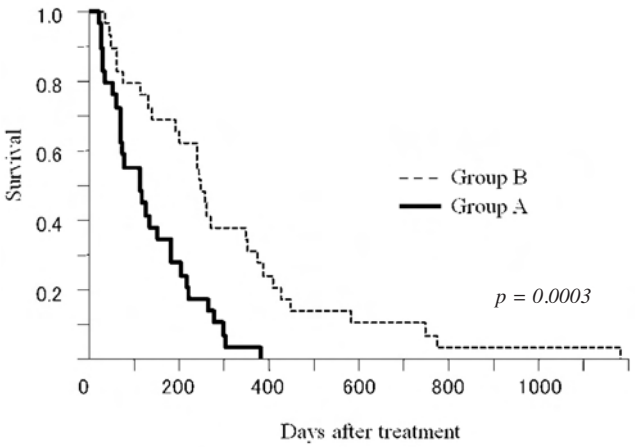

Fig. 3

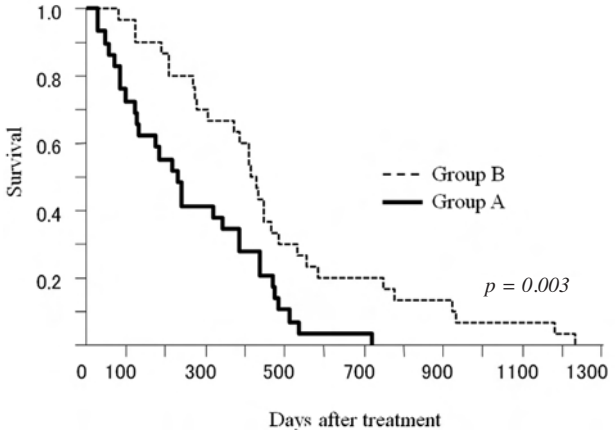

Figure 1. — Study groups.

Figure 2. — Disease-specific progression-free survival per grroup. Survival curves drawn by the Kaplan-Meier method.

Figure 3. — Disease-specific overall survival per group. Survival curves drawn by the Kaplan-Meier method.

Follow-up examinations were done every month. All follow-up examinations included pelvic examination, transvaginal ultrasonography, tumor marker CA125 antigen assay, and identification of late complications. Every six months, we obtained a computed tomography scan of the abdomen and a chest X-ray film. For each patient, survival was calculated from the date therapy was started to the date of the last follow-up examination. Survival curves were drawn according to the Kaplan-Meier method. Differences in patient characteristics, progression-free survival time, overall survival time, and toxic events were evaluated by exploratory global chi-square test; p values < 0.05 were considered statistically significant.

Treatment schedule

For the CPT-11/CDDP regimen, patients received 60 mg/m^2 irinotecan on days 1, 8, and 15, and 60 mg/m^2 CDDP on day 1. Cycles were repeated every 28 days. For the CPT-11/NDP regimen, patients received 60 mg/m^2 CPT-11 on days 1 and 8, and 80 mg/m^2 NDP on day 1. Cycles were repeated every 28 days. For the DP regimen, patients received 60 mg/m^2 docetaxel and 60 mg/m^2 CDDP on day 1. Cycles were repeated every 21 days. Cycles were repeated in the absence of progressive disease or unacceptable toxicity.

Evaluation of response and safety

Tumor response was evaluated according to the RECIST guidelines. Complete response was defined as the complete disappearance of all evident disease for at least four weeks. Partial response was defined as a > 30% decrease in the product of perpendicular diameters for each measurable lesion without the appearance of a new lesion or increase in evaluable lesions or markers for at least four weeks. Progressive disease was defined as a > 20% increase in the product of perpendicular diameters of any measurable lesion or the appearance of any new disease. Stable disease was defined as disease for which none of these criteria were met. A progression-free interval was defined as the period of time from the day the study drug was administered until disease progression was observed. Survival was defined as the period from the first day of study drug administration to the day of death or last follow-up examination.

The severity of adverse events was assessed according to the Common Terminology for Adverse Events (CTCAE), version 3.0.

Results

Study population

Patient characteristics are shown per group in Table 1. Mean age of the patients was 57.4 years (range, 39-78 years). Overall, the numbers of patients with ovarian carcinoma, tubal carcinoma, and peritoneal carcinoma were 55, 3, and 2, respectively. The numbers of patients with serous adenocarcinoma and clear cell adenocarcinoma,

Table 1. — *Patient characteristics per study group*.

	Group A (n = 29)	Group B (n = 31)	*p* value*
Age (years)	29-72 (mean: 55.9)	44-76 (mean: 58.8)	
Tumor site			
Ovary	27	28	.6958
Fallopian tube	2	1	.5115
Peritoneum	–	2	.1000
Histotype			
Serous	18	24	.1936
Clear cell	8	4	.1528
Mixed	2	2	.9450
Other	1	1	.9617
No. of chemotherapy courses	1-7 (mean: 3.0)	1-8 (mean: 4.3)	

* All *p* values were calculated by chi-square test for population.

Table 2. — *Responses to treatment per study group*.

	Group A (n = 29) No. (%)		Group B (n = 31) No. (%)	
Complete response	0	(10.3)	5	(41.9)
Partial response	3		8	
Stable disease	3		5	
Progressive disease	23	(79.3)	13	(41.9)

Table 3. — *Chemotherapy-related adverse events (grade 3-4 toxicity)*.

Toxicity	Group A		Group B		
	No. of patients	Incidence (%)	No. of patients	Incidence (%)	*p* value*
Leukopenia	14	48.3	16	51.6	.7961
Neutropenia	19	65.5	22	71.0	.6502
Thrombocytopenia	1	3.4	2	6.5	.5898
Nausea/vomiting	1	3.4	–	–	.2250
Diarrhea	1	3.4	–	–	.2250

* All *p* values were calculated by chi-square test for population.

were 42, and 12, respectively. The remaining six patients comprised four with mixed-epitherial carcinoma, one with transitional carcinoma, and one with squamous cell carcinoma. Thirty-three of the 60 patients had been subjected to one chemotherapy regimen previously, 24 patients had been subjected to two regimens, and the remaining three patients had been subjected to more than three regimens. There was no significant difference in patient characteristics between the two groups, except with respect to the number of patients who had undergone more than three chemotherapy regimens. Overall, patients been subjected to 1-8 courses (mean, 3.65 courses) of second-line combination chemotherapy.

Response to treatment

Responses to treatment are shown per group in Table 2. The response rate in Group A was 10.3%, (partial response, n = 3). In group B, the response rate was 41.9% (partial response, n = 5; complete response, n = 8). In Group A patients given CPT-11, the complete response rate was 0.0%, and the partial response rate was 15.0%. In Group B patients given CPT-11, the complete response rate was 14.3%, and the partial response rate was 28.6%. In Group A patients given DTX, both the complete response rate and partial response rate were 0.0%. In Group B, the respective response rates were 18.2% and 18.2%.

Survival

Disease-specific progression-free survival curves are shown per group in Figure 2. A significant difference (p = 0.00003) was noted between Group A and Group B in progression-free survival. Mean time to disease progression was 3.83 months in Group A and 8. 0 months in Group B *(p = 0.006)*. Overall disease-specific survival curves are shown per group in Figure 3. A significant difference in overall disease-specific survival was noted between the two groups (p = 0.003). Mean overall survival time was 7.3 months in Group A and 9.37 months in Group B (p = 0.028).

Adverse events

Chemotherapy-related adverse events are shown per group in Table 3. There were no statistical differences in the incidence of adverse events between the two groups. The most common CTCAE Grade 2 or above adverse events were due to hematological toxicity: leukopenia and neutropenia. Grade 3-4 leukopenia occurred in 38.5% of patients treated with CPT-11 and in 71.4% of patients treated with DTX *(p = 0.0137)*. Grade 3-4 neutropenia occurred in 59.0% and 85.7% of patients, respectively *(p = 0.0270)*. Bone marrow suppression was more severe in patients treated with DTX than in patients treated with CPT-11.

Discussion

Recurrent epithelial ovarian carcinoma is usually incurable. It has been shown that, upon relapse, the probability of a response to re-treatment with platinum-based chemotherapy depends on the platinum-free interval [9]. Retrospective studies of platinum-based second-line therapies have led to the identification of two subgroups of patients with recurrent ovarian cancer: those with platinum-refractory disease and those with platinum-sensitive disease [9, 11].

There has been no report that combination chemotherapy provides an advantage over single-agent chemotherapy in patients with platimun-refractory disease [22, 23]. In the present study, only 10.3% of platinum-refractory cases responded to second-line combination-chemotherapy. Generally, single-agent chemotherapies have been used in such patients in an effort to minimize toxicity and preserve a patient's quality of life. Several randomized trials have compared outcomes of single agents in this patient population. In general, these studies showed no statistical difference, and no clear benefit of any one agent has been established [24-27].

There have been several reports that platinum-based combination chemotherapy, in comparison to single-

agent therapy, prolongs overall survival and progression-free survival in platinum-sensitive patients [13, 19-21, 28]. In addition, there have been several reports comparing combination chemotherapies among platinum-sensitive patients. In the International Collaborative Ovarian Neoplasm 4 (ICON 4) and Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer -2.2 randomized trial, more than 800 platinum-sensitive patients with recurrent ovarian carcinoma were randomly assigned to paclitaxel plus platinum or conventional platinum-based chemotherapy. The paclitaxel plus platinum combination improved overall survival and progression-free survival among patients with relapsed platinum-sensitive ovarian cancer [20]. Phisterer *et al*. studied 356 platinum-sensitive patients with recurrent ovarian carcinoma who were randomly assigned to gemcitabine plus carboplatin or carboplatin treatment. They reported that gemcitabine plus carboplatin improved the progression-free survival of these patients [13]. So, for platinum-sensitive patients with recurrent disease, platinum with taxanes is recommended as first-line combination chemotherapy. Moreover, in the S-P's Caelyx in Platinum-Sensitive Ovarian Cancer study conducted by the Gynecologic Cancer Intergroup, over 900 platinum-sensitive patients with recurrent ovarian carcinoma were randomly assigned to treatment with liposomal doxorubicin plus carboplatin or paclitaxel plus carboplatin. The liposomal doxorubicin plus carboplatin combination chemotherapy proved favorable in terms of progression-free survival and quality of life [29].

However, when platinum-sensitive patients receive the first-line combination chemotherapy for treatment of recurrent diseases but a second response is observed, there has not been any debate regarding the next chemotherapy option. It is thought that monochemotherapy is appropriate for such patients, as in platinum-refractory patients. It is noteworthy, however, that 41.9% of our platinum-sensitive patients (Group B) responded to second-line combination chemotherapy. These patients show a high sensitivity to chemotherapy in general, so they respond to the subsequent combination chemotherapy.

Generally, patients who have already received the paclitaxel-platinum combination as primary treatment are at risk of severe cumulative neurotoxicity if this combination is used for relapse [30]. Phisterer *et al*. treated platinum-sensitive patients with carboplatin or gemcitabine plus carboplatin. Grade 3-4 hematologic toxicities were significantly more frequent in the combination arm; neutropenia was the predominant toxicity, but the toxicity profile was considered acceptable [13]. Martin *et al*. treated platinum-sensitive patients with carboplatin or paclitaxel plus carboplatin and found no significant between-group difference in grade 3-4 hematologic toxicities, but mucositis, myalgia/arthralgia, and peripheral neuropathy were more frequent in the combination arm [28]. In the present study, neutropenia was the major hematologic toxicity associated with both treatments. Hematologic toxicity was more severe with the DTX regimen than with the CPT-11 regimen, but there were no differences in complications between Group A and Group B. The regimen used in the present study was also found to be safe and well tolerated, and adverse events were mild to moderate in the majority of patients.

In conclusion, it is likely that the second-line combination chemotherapy for TC-refractory ovarian cancer differs in effectiveness between platinum-sensitive and platinum-refractory patients, depending on whether cancer was previously sensitive to chemotherapy. If there is a history of response to chemotherapy, multi-agent chemotherapy is worth considering even after TC failure. When there is no history of previous success in chemotherapy, the efficacy of multi-agent chemotherapy as second-line chemotherapy is expected to be low, suggesting the use of monochemotherapy.

References

[1] McGuire W.P., Hoskins W.J., Brady M.F., Kucera P.R., Partridge E.E., Look K.Y. *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.

[2] Neijt J.P., Engelholm S.A., Tuxen M.K., Sorensen P.G., Hansen M., Sessa C. *et al*.: "Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer". *J. Clin. Oncol.,* 2000, *18*, 3084.

[3] Ozols R.F., Bundy B.N., Greer B.E., Fowler J.M., Clarke-Pearson D., Burger R.A. *et al*.: "Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected Stage III ovarian cancer: a Gynecologic Oncology Group study". *J. Clin. Oncol.,* 2003, *21,* 3194.

[4] Johnson S.R.: "Ovarian cancer: review of the National Institute for Clinical Excellence (NICE) guidance recommendations". *Cancer Invest.,* 2004, *22*, 730.

[5] du Bois A., Lück H.J., Meier W., Adams H.P., Mobus V., Costa S. *et al*.: "A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer". *J. Natl. Cancer Inst.,* 2003, *95*, 1320.

[6] Cannistra S.A.: "Cancer of the ovary". *N. Engl. J. Med*., 1993, *329*, 1550.

[7] Alberts D.S., Mason-Liddil N.: "Carboplatin in the treatment of ovarian cancer". Semin. Oncol., 1989, *16* (2 suppl. 5), 19.

[8] Gershenson D.M., Kavanagh J.J., Copeland L.J., Stringer C.A., Morris M., Wharton J.T.: "Re-treatment of patients with recurrent epithelial ovarian cancer with cisplatin based chemotherapy". *Obstet. Gynecol.,* 1989, *73,* 709.

[9] Markman M., Rothman R., Hakes T., Reichman B., Hoskins W., Rubin S. *et al*.: "Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin". *J Clin Oncol.,* 1991, 9, 389.

[10] Weiss G., Green S., Alberts D.S., Thigpen J.T., Hines H.E., Hanson K. *et al*.: "Second-line treatment of advanced measurable ovarian cancer with iproplatin: a Southwest Oncology Group study". *Eur. J. Cancer,* 1991, *27*, 135.

[11] Gore M.E., Fryatt I., Wiltshaw E. *et al*.: "Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds". *Gynecol. Oncol.,* 1990, *36*, 207.

[12] Zanaboni F., Scarfone G., Presti M. *et al*.: "Salvage chemotherapy for ovarian cancer recurrence: weekly cisplatin in combination with epirubicin or etoposide". Gynecol. Oncol., 1991, *43*, 24.

[13] Phisterer J., Vergote I., Du Bois A. *et al*.: "Combination therapy with gemcitabine and carboplatin in recurrent ovarian cancer". *Int. J. Gynecol. Cancer,* 2005, *15* (suppl. 1), 36.

[14] Ozols R.F., Schwartz P.E., Eifel P.J.: "Treatment of advanced-stage ovarian cancer". In: DeVita V.T., Hellman S., Rosenberg S.A. *et al*. (eds.). Cancer: Principles and Practice of Oncology. Philadelphia, PA, Lippincott-Raven, 1997, 1514.

[15] Alberts D.S.: "Treatment of refractory and recurrent ovarian cancer". *Semin. Oncol.,* 1999, *26* (1 suppl. 1), 8.

[16] McGuire W.P., Blessing J.A., Bookman M.A., Lentz S.S., Dunton C.J.: "Topotecan has substantial antitumor activity as first-line salvage therapy in platinum-sensitive epithelial ovarian carcinoma: a Gynecologic Oncology Group study". *J. Clin. Oncol.,* 2000, *18,* 1062.

[17] Eisenhauer E.A., Vermorken J.B., van Glabbeke M.: "Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: a multivariate analysis of 704 patients". *Ann. Oncol.,* 1997, *8,* 963.

[18] Ozols R.F.: "Treatment of recurrent ovarian cancer: increasing options "recurrent" results". *J. Clin. Oncol.,* 1997, *15,* 2177.

[19] Bolis G., Scarfone G., Giardina G., Villa A., Mangili G., Melpignano M. *et al*.: "Carboplatin alone vs carboplatin plus epidoxorubicin as second-line therapy for cisplatin- or carboplatin-sensitive ovarian cancer". *Gynecol. Oncol.,* 2001, *81,* 3.

[20] Parmar M.K., Ledermann J.A., Colombo N., du Bois A., Delalove J.F., Kristensen G.B. *et al*.: "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.

[21] Bookman M.: "Developmental chemotherapy in advanced ovarian cancer: incorporation of newer cytotoxic agents in a phase III randomized trial of the Gynecologic Oncology Group (GOG-0182)". *Semin. Oncol.,* 2002, *29* (1 suppl. 1), 20.

[22] Buda A., Floriani I., Rossi R., Colombo N., Torri V., Conte P.F. *et al*.: "Randomised controlled trial comparing single agent paclitaxel vs epidoxorubicin plus paclitaxel in patients with advanced ovarian cancer in early progression after platinum-based chemotherapy: an Italian Collaborative Study from the Mario Negri Institute, Milan, G.O.N.O. (Gruppo Oncologico Nord Ovest) group and I.O.R. (Instituto Oncologico Romagnolo) group". *Br. J. Cancer,* 2004, *90,* 2112.

[23] Sehouli J., Sommer H., Klare P. et al.: "A randomized multicenter phase III trial of topotecan monotherapy versus topotecan + etoposide versus topotecan + gemcitabine for second-line treatment of recurrent ovarian cancer". *J. Clin. Oncol*., ASCO Annual Meeting Proceeding, 2006, *24* (20 suppl.), 5030.

[24] Gore M., Oza A., Rustin G., Malfetano J., Calvert H., Clarke-Pearson D. *et al*.: "A randomized trial of oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer". *Eur. J. Cancer,* 2002, *38,* 57.

[25] Gordon A., Fleagle J.T., Guthrie D., Parkin D.E., Gore M.E., Lacave A.J.: "Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan". *J. Clin. Oncol.,* 2001, *19*, 3312.

[26] ten Bokkel Huinink W., Gore M., Carmichael J., Gordon A., Malfetano J., Hudson I. *et al*.: "Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer". *J. Clin. Oncol.,* 1997, *15,* 2183.

[27] ten Bokkel Huinink W., Lane S., Ross G., International Topotecan Study Group: "Long-term survival in a phase III, randomized study of topotecan versus paclitaxel in advanced epithelial ovarian cancer". *Ann. Oncol*., 2004, *15*, 100.

[28] Gonzalez-Martin A.J., Calvo E., Bover I., Rubio M.J., Arcusa A., Casado A. *et al*.: "Randomized phase II trial of carboplatin versus paclitaxel and carboplatin in platinum-sensitive recurrent advanced ovarian carcinoma: a GEICO (Groupo Espanol de Investigation en Cancer de Ovario) study". *Ann. Oncol.,* 2005, *16,* 749.

[29] Pujade-Lauraine E., Uwe Wagner, Aavall-Lundqvist E., Gebski V., Heywood M., Vasey P.A. *et al*.: "Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse". *J. Clin Oncol.,* 2010, *28*, 3323.

[30] Armstrong D.K.: "Relapsed ovarian cancer: challenges and management strategies for a chronic disease". *Oncologist,* 2002, *7* (suppl. 5), 20.

Address reprint requests to:
T. OTA, M.D.
Department of Gynecology
Cancer Institute Hospital
Ariake 3-10-6, Koutou-ku, Tokyo
135-8550 (Japan)
e-mail: tsuyoshi@ota.name