Table 1. Patients' characteristics

Characteristic	No. of patients	%
Registered patients	28	–
Eligible patients	27	–
Stage		
III	24	88.9
IV	3	11.1
Histology		
Serous	23	85.2
Endometrioid	2	7.4
Clear cell	1	3.7
Undifferentiated	1	3.7
Residual disease		
0	4	14.8
0–1 cm	6	22.2
1–2 cm	4	14.8
>2 cm	13	48.1

it was decided to determine RD taking into account the toxicities of all cycles, the necessity of G-CSF support, the actual dose delivery and efficacy.

Hematological Toxicity

The hematological toxicity results are summarized in Table 2. The major toxicities observed were neutropenia and leukopenia. Grade 4 neutropenia was observed frequently even during the first course of chemotherapy [85% (23/27)] and almost all patients developed grade 4 neutropenia during all courses of chemotherapy [96% (26/27)]. The dose level was not correlated with the frequency of neutropenia (100% in level 1 and 83% in level 4 during the first course of chemotherapy). Grade 4 leukopenia was observed in 44% (12/27) of patients during the first course and in 52% (14/27) of patients during all courses of chemotherapy. The toxicity did not seem to increase from the second to sixth courses of chemotherapy. However, the frequency of grade 4 leukopenia was correlated with the dose level during the first course [22% (2/9) in level 1 to 83% (5/6) in level 4] and all courses of chemotherapy [22% (2/9) in level 1 to 83% (5/6) in level 4]. Among these grade 4 hematological toxicities observed during the first course of chemotherapy, toxicity developed by one patient in level 4 matched the dose-limiting toxicity criterion (a). As for other hematological toxicity, grade 3 anemia was rarely observed during the first course of chemotherapy [11% (3/27)]; however, nearly half of patients developed grade 3 anemia during all courses of chemotherapy [44% (12/27)]. Grade 4 thrombocytopenia was never observed during the first course of chemotherapy and only one patient developed grade 4 thrombocytopenia during all courses of chemotherapy [4% (1/27)].

Table 2. Hematological toxicity

Toxicity	No.(%) of grade 3/grade 4 toxicity			
	Level 1 (n = 9)	Level 2 (n = 6)	Level 3 (n = 6)	Level 4 (n = 6)
(A) During first course of chemotherapy				
Leukopenia	6 (67)/2 (22)	4 (67)/2 (33)	1 (17)/3 (50)	1 (17)/5 (83)
Neutropenia	0 (0)/9 (100)	1 (17)/4 (67)	0 (0)/5 (83)	1 (17)/5 (83)
Anemia	1 (11)/NA	0 (0)/NA	1 (17)/NA	1 (17)/NA
Thrombocytopenia	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
(B) During all courses of chemotherapy				
Leukopenia	6 (67)/2 (22)	3 (50)/3 (50)	1 (17)/4 (67)	1 (17)/5 (83)
Neutropenia	0 (0)/9 (100)	1 (17)/5 (83)	0 (0)/6 (100)	0 (0)/6 (100)
Anemia	2 (22)/NA	2 (33)/NA	6 (100)/NA	2 (33)/NA
Thrombocytopenia	0 (0)/0 (0)	1 (17)/0 (0)	2 (33)/0 (0)	1 (17)/1 (17)

Table 3. Non-hematological toxicity

Toxicity	No.(%) of grade 2/grade 3 toxicity			
	Level 1 (n = 9)	Level 2 (n = 6)	Level 3 (n = 6)	Level 4 (n = 6)
(A) During first course of chemotherapy				
Nausea and vomiting	2 (22)/1 (11)	2 (33)/1 (17)	3 (50)/0 (0)	2 (33)/1 (17)
Diarrhea	1 (11)/1 (11)	2 (33)/0 (0)	0 (0)/0 (0)	1 (17)/1 (17)
Alopecia	0 (0)/NA	0 (0)/NA	1 (17)/NA	2 (33)/NA
Neuropathy-sensory	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Hypersensitivity	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Renal toxicity	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Febrile neutropenia	NA/1 (11)	NA/0 (0)	NA/2 (33)	NA/2 (33)
(B) During all courses of chemotherapy				
Nausea and vomiting	5 (55)/1 (11)	2 (33)/1 (17)	4 (67)/0 (0)	4 (67)/1 (17)
Diarrhea	1 (11)/1 (11)	2 (33)/0 (0)	0 (0)/0 (0)	0 (0)/2 (33)
Alopecia	8 (88)/NA	5 (83)/NA	5 (83)/NA	5 (83)/NA
Neuropathy-sensory	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	1 (17)/0 (0)
Hypersensitivity	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Renal toxicity	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)	0 (0)/0 (0)
Febrile neutropenia	NA/2 (22)	NA/0 (0)	NA/2 (33)	NA/2 (33)

Non-Hematological Toxicity

The results of non-hematological toxicity are listed in Table 3. Generally, non-hematological toxicity was mild or moderate. The observed grade 3 toxicities during the first course or all courses of chemotherapy were nausea and vomiting in 11% (3/27) or 11% (3/27), diarrhea in 7% (2/27) or 11% (3/27) and febrile neutropenia in 19% (5/27) or 22% (6/27), respectively. The frequency of above grade 3 toxicities did not increase during the second to sixth courses of chemotherapy and was not correlated with the dose levels. Among these grade 3 toxicities observed during the first course of chemotherapy,

Table 4. Clinical response

Clinical response	Level 1 (n = 9)	Level 2 (n = 6)	Level 3 (n = 6)	Level 4 (n = 6)	Total
Complete response	4	1	4	3	12
Partial response	1	2	0	1	4
No change	0	0	0	0	0
Progressive disease	0	0	2	1	3
Not evaluable	4	3	0	1	8
Response rate (%)	100 (5/5)	100 (3/3)	67 (4/6)	80 (4/5)	84 (16/19)

two cases of diarrhea, one in level 1 and one in level 4 and one febrile neutropenia in level 4 matched the dose-limiting toxicity criteria (d) and (b). Other than these toxicities, alopecia was the most frequently observed toxicity: 85% (23/27) of patients developed grade 2 alopecia during all courses of chemotherapy. Grade 2/3 hypersensitivity and any grade renal toxicity (rise of serum creatinine) were not observed during the study. It was noteworthy that grade 2/3 sensory neuropathy was not observed during the first course of chemotherapy and only one patient [4% (1/27)] developed grade 2 sensory neuropathy during all courses of chemotherapy.

Clinical Response

Eight patients had no measurable disease at entry. In the other 19 patients with two-dimensionally measurable disease, the response to chemotherapy was evaluated (Table 4). Twelve patients achieved complete response and four achieved partial response. The overall response rate was 84% (16/19) among patients with measurable disease. The remaining three patients had progressive disease. The response rate at dose levels 1–4 was 100, 100, 67 and 80%, respectively, suggesting no correlation between the dose level and response rate.

Recommended Dose

Table 5 summarizes the characteristics of chemotherapy at each level. In level 4, the majority of cycles [91% (30/33)] required G-CSF support and more than 30% of chemotherapy cycles required some modification in the dose or starting date of chemotherapy. However, chemotherapy could be continued until the planned cycle was completed or disease progression in most cases [83% (5/6)]. Moreover, 93.4% of the planned doses of agents could be administered at level 4. Considering all the factors, such as hematological and non-hematological toxicities, clinical responses and actual dose deliveries at dose level 4, RD for further study was decided as dose level 4 consisting of 110 mg/m^2 of PTX, 50 mg/m^2 of DOX and 75 mg/m^2 of CDDP.

DISCUSSION

In this study, we evaluated the safety and efficacy of a combination regimen of PTX, DOX and CDDP (TAP) as first-line chemotherapy for AOC. Because of the bone marrow toxicity of both CBDCA and DOX, CDDP seems to be safer than CBDCA to combine with DOX as a platinum analog. On the other hand, the combination of CDDP and PTX may produce severe and irreversible neurotoxicity (2,16,17). To avoid this adverse effect and to reduce cardiac toxicity, PTX was administered in a 24 h continuous infusion (18). The PTX dose was set at 110 mg/m^2 as the minimum dose at which sufficient response could be expected, because there is no dose–response relationship in a range of 110 mg/m^2 or more (19). The dose of CDDP was decided as the standard dose of 75 mg/m^2 (20). The DOX dose was increased from 20 to 50 mg/m^2 and was expected to improve efficacy over the standard combination of PTX and platinum. To avoid excessive toxicity, PTX was administered following DOX (21,22) and CDDP was administered following PTX (23). The regimen therefore consisted of 20–50 mg/m^2 increasing doses of DOX followed by 24 h infusion of 110 mg/m^2 of PTX followed by 75 mg/m^2 of CDDP.

Concerning the safety of the regimen, the three-drug combination regimen seemed to be sufficiently safe to use as first-line chemotherapy for patients with ovarian cancer. The major toxicities observed in our study were neutropenia and leukopenia. Grade 4 neutropenia and leukopenia were observed in 85% (23/27) and 44% (12/27) in the first course of chemotherapy. However, these toxicities rarely lasted long enough to be counted as DLT and were not cumulative in the 2nd to 6th courses of chemotherapy. Thus, these hematological toxicities seemed manageable. Moreover, non-hematological toxicities were generally mild or moderate. The grade 3 toxicities observed were nausea and vomiting in 11% (3/27), diarrhea in 11% (3/27) and febrile neutropenia in 22% (6/27), during all courses

Table 5. Summary of chemotherapies

	Level 1	Level 2	Level 3	Level 4
No. of cycles administered	48	36	32	33
Percentage of cycles required				
G-CSF use	60 (29/48)	72 (26/36)	66 (21/32)	91 (30/33)
Dose reduction	13 (5/39)	7 (2/30)	15 (4/26)	33 (9/27)
Treatment delay	21 (8/39)	20 (6/30)	8 (2/26)	30 (8/27)
Percentage of patients who completed chemotherapy*	67 (6/9)	100 (6/6)	100 (6/6)	83 (5/6)
Average drug administration				
PTX(mg/m^2)	106	108	107	103
DOX(mg/m^2)	19	29	39	47
CDDP(mg/m^2)	72	74	73	70
Percentage of actual/planned doses	96.4	98.2	97.2	93.4

*All six cycles of chemotherapy were completed or chemotherapy was discontinued because of disease progression.

of chemotherapy. Grade 3 sensory neuropathy was not observed during all courses of chemotherapy. To our knowledge, seven phase I or I/II studies (10,24–29), evaluating the value of anthracyclines in a taxane and platinum-based regimen for previously untreated AOC, have been published. The major toxicities observed throughout the studies were hematological toxicities, such as neutropenia, leukopenia and thrombocytopenia. In particular, neutropenia was reported in 100% in some studies (25,27,28). However, the toxicity was readily managed using G-CSF and was rarely complicated with serious infection or sepsis. Non-hematological toxicities, excluding nausea, vomiting and alopecia, were generally mild and manageable. No severe cardiac toxicity or neuropathy was observed throughout the previous studies.

As for the efficacy of the triplet combination in our study, a response rate (RR) of 84% (16/19), including 63% (12/19) complete response (CR), was observed. Even in level 1, 100% RR was achieved and there was no correlation between the dose level and response rate. In the previous studies, that using docetaxel (DOC) as the taxane (28) showed a relatively lower response rate of 36%, but studies using PTX as the taxane showed a higher response rate of 83–100%. In studies using PTX, there were no apparent differences in the response rate between studies using CDDP (86–100%) (25,26) and those using CBDCA (83–100%) (10,24,29) as platinum compound and between studies using DOX (100%) (24,25) and those using EpiDOX (83–86%) (10,26,29) as anthracycline.

In summary, the combination regimen of DOX with PTX and CDDP is highly active and hematological toxicities are readily manageable and non-hematological toxicities, including cardiac toxicity and sensory neuropathy, were mild or moderate. From our study and previous studies, we conclude that the addition of anthracyclines to PTX plus a platinum-based regimen may provide an effective and safe regimen for patients with untreated ovarian cancer. However, the hematological toxicities seem to be relatively severe compared with those reported with a PTX/CBDCA combination (3,30,31). At present, AGO–GINECO (Arbeitsgemeinschaft Gynäkologische Onkologie–Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens) (32) and NSGO–EORTC–NCIC CTG (Nordic Society of Gynecological Oncology–European Organization for Research and Treatment of Cancer–National Cancer Institute of Canada Clinical Trials Group) (33) are conducting phase III studies comparing epirubicin/paclitaxel/carboplatin vs. paclitaxel/carboplatin. To assess the usefulness of anthracyclines, the results of these studies are awaited.

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References

1. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1–6.
2. Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, et al. Randomized intergroup trial of cisplatin–paclitaxel versus cisplatin–cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000;92:699–708.
3. Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, 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;21:3194–200.
4. Nguyen HN, Averette HE, Hoskins W, Sevin BU, Penalver M, Steren A. National survey of ovarian carcinoma. VI. Critical assessment of current International Federation of Gynecology and Obstetrics staging system. *Cancer* 1993;72:3007–11.
5. Omura GA, Bundy BN, Berek JS, Curry S, Delgado G, Mortel R. Randomized trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol* 1989;7:457–65.
6. Cyclophosphamide plus cisplatin versus cyclophosphamide, doxorubicin and cisplatin chemotherapy of ovarian carcinoma: a meta-analysis. The Ovarian Cancer Meta-Analysis Project. *J Clin Oncol* 1991;9:1668–74.
7. Fanning J, Bennett TZ, Hilgers RD. Meta-analysis of cisplatin, doxorubicin and cyclophosphamide versus cisplatin and cyclophosphamide chemotherapy of ovarian carcinoma. *Obstet Gynecol* 1992;80:954–60.
8. A'Hern RP, Gore ME. Impact of doxorubicin on survival in advanced ovarian cancer. *J Clin Oncol* 1995;13:726–32.
9. Tobinai K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. *Jpn J Clin Oncol* 1993;23:250–7.
10. du Bois A, Luck HJ, Bauknecht T, Meier W, Richter B, Kuhn W, et al. First-line chemotherapy with epirubicin, paclitaxel and carboplatin for advanced ovarian cancer: a phase I/II study of the Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group. *J Clin Oncol* 1999;17:46–51.
11. Siddiqui N, Boddy AV, Thomas HD, Bailey NP, Robson L, Lind MJ, et al. A clinical and pharmacokinetic study of the combination of carboplatin and paclitaxel for epithelial ovarian cancer. *Br J Cancer* 1997;75:287–94.
12. Bolis G, Scarfone G, Villa A, Acerboni S, Siliprandi V, Guarnerio P. A phase I trial with fixed-dose carboplatin and escalating doses of paclitaxel in advanced ovarian cancer. *Semin Oncol* 1997;24, No 1, Suppl 2:23–5.
13. Huizing MT, van Warmerdam LJ, Rosing H, Schaefers MC, Lai A, Helmerhorst TJ, et al. Phase I and pharmacologic study of the combination paclitaxel and carboplatin as first-line chemotherapy in stage III and IV ovarian cancer. *J Clin Oncol* 1997;15:1953–64.
14. ten Bokkel Huinink WW, Veenhof C, Huizing M, Rodenhuis S, Helmerhorst T, Dubbelman R, et al. Carboplatin and paclitaxel in patients with advanced ovarian cancer: a dose-finding study. *Semin Oncol* 1997;24, No 1, Suppl 2:31–3.
15. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
16. Rowinsky EK, Chaudhry V, Forastiere AA, Sartorius SE, Ettinger DS, Grochow LB, et al. Phase I and pharmacologic study of paclitaxel and cisplatin with granulocyte colony-stimulating factor: neuromuscular toxicity is dose-limiting. *J Clin Oncol* 1993;11:2010–20.
17. Chaudhry V, Rowinsky EK, Sartorius SE, Donehower RC, Cornblath DR. Peripheral neuropathy from taxol and cisplatin combination chemotherapy: clinical and electrophysiological studies. *Ann Neurol* 1994;35:304–11.
18. Smith RE, Brown AM, Mamounas EP, Anderson SJ, Lembersky BC, Atkins JH, et al. Randomized trial of 3-hour versus 24-hour infusion of high-dose paclitaxel in patients with metastatic or locally advanced breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-26. *J Clin Oncol* 1999;17:3403–11.
19. Rowinsky EK, Mackey MK, Goodman SN. Meta analysis of paclitaxel dose–response and dose–intensity in recurrent or refractory ovarian cancer. *Proc Am Soc Clin Oncol* 1996;15:Meeting Abstract.

20. Kaye SB, Paul J, Cassidy J, Lewis CR, Duncan ID, Gordon HK, et al. Mature results of a randomized trial of two doses of cisplatin for the treatment of ovarian cancer. Scottish Gynecology Cancer Trials Group. *J Clin Oncol* 1996;14:2113–9.
21. Sledge GW Jr, Robert N, Sparano JA, Cobeligh M, Goldstein LJ, Neuberg D, et al. Paclitaxel (taxol)/doxorubicin combinations in advanced breast cancer: the Eastern Cooperative Oncology Group experience. *Semin Oncol* 1994;21:15–8.
22. Sledge GW Jr, Robert N, Sparano JA, Cogleigh M, Goldstein LJ, Neuberg D, et al. Eastern Cooperative Oncology Group studies of paclitaxel and doxorubicin in advanced breast cancer. *Semin Oncol* 1995;22:105–8.
23. Rowinsky EK, Gilbert MR, McGuire WP, Noe DA, Grochow LB, Forastiere AA, et al. Sequences of taxol and cisplatin: a phase I and pharmacologic study. *J Clin Oncol* 1991;9:1692–703.
24. Hill M, Macfarlane V, Moore J, Gore ME. Taxane/platinum/anthracycline combination therapy in advanced epithelial ovarian cancer. *Semin Oncol* 1997;24, No 1, Suppl 2:34–7.
25. Naumann RW, Alvarez RD, Omura GA, Segars E, Kilgore LC, Partridge EE. A phase I study of paclitaxel, doxorubicin and cisplatin in patients with previously untreated epithelial ovarian cancer. *Gynecol Oncol* 1998;71:450–3.
26. Papadimitriou CA, Moulopoulos LA, Vlahos G, Voulgaris Z, Kiosses E, Georgoulias N, et al. Paclitaxel, cisplatin and epirubicin first-line chemotherapy in stage III and IV ovarian carcinoma: long-term results of a phase II study. *Cancer* 2000;89:1547–54.
27. Gregory RK, Hill ME, Moore J, A'Hern RP, Johnston SR, Blake P, et al. Combining platinum, paclitaxel and anthracycline in patients with advanced gynaecological malignancy. *Eur J Cancer* 2000;36:503–7.
28. O'Neill VJ, Kaye SB, Reed NS, Paul J, Davis JA, Vasey PA. A dose-finding study of carboplatin–epirubicin–docetaxel in advanced epithelial ovarian cancer. *Br J Cancer* 2002;86:1385–90.
29. Romanini A, Tanganelli L, Carnino F, Fanucchi A, Lionetto R, Pastorino S, et al. First-line chemotherapy with epidoxorubicin, paclitaxel and carboplatin for the treatment of advanced epithelial ovarian cancer patients. *Gynecol Oncol* 2003;89:354–9.
30. Neijt JP, Engelholm SA, Witteveen PO, Tuxen MK, Sorensen PG, Hansen M, et al. Paclitaxel (175 mg/m^2 over 3 h) with cisplatin or carboplatin in previously untreated ovarian cancer: an interim analysis. *Semin Oncol* 1997;24, No 5, Suppl 15:36–9.
31. du Bois A, Luck HJ, Meier W, Mobus V, Costa S, Richter B, et al. Carboplatin/paclitaxel versus cisplatin/paclitaxel as first-line chemotherapy in advanced ovarian cancer: an interim analysis of a randomized phase III trial of the Arbeitsgemeinschaft Gynakologische Onkologie Ovarian Cancer Study Group. *Semin Oncol* 1997;24, No 5, Suppl 15: 44–52.
32. du Bois A, Weber B, Pfisterer J, Goupil A, Wagner U, Barats J, et al. Epirubicin/paclitaxel/carboplatin (TEC) vs. paclitaxel/carboplatin (TC) in first-line treatment of ovarian cancer FIGO stages IIb/IV. Interim results of an AGO/GINECO Intergroup Phase III trial. *Proc Am Soc Clin Oncol* 2001;20:Abstract 805.
33. Kristensen G, Vergote I, Stuart G, Izqiuerdo Delso M, Mirza MR, Aavall-Lundquist E, et al. First line treatment of ovarian cancer FIGO stages IIb–IV with paclitaxel/epirubicin/carboplatin (TEC) vs. paclitaxel/carboplatin (TC). Interim results of an NSGO–EORTC–NCIC CTG Gynecological Cancer Intergroup phase III trial. *Proc Am Soc Clin Oncol* 2002;21:Abstract 805.

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The effect of single weekly paclitaxel in heavily pretreated patients with recurrent or persistent advanced ovarian cancer

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Abstract

Objectives. We have reported that single weekly paclitaxel has moderate activity in heavily pretreated ovarian cancer patients and is associated with a favorable toxicity profile. The purpose of this study was to reconfirm the effect of weekly paclitaxel in more number of cases.

Methods. Although 39 patients were enrolled, 37 patients with recurrent or persistent ovarian cancer previously treated with between one and three chemotherapeutic regimens containing platinum were eligible. Patients had measurable or assessable disease defined by clinical exam, radiographic studies, or serum CA 125. One cycle of treatment consisted of paclitaxel 80 mg/m^2/week in 1-h infusion, 3 weeks on, 1 week off, and repeated at least twice. Two patients were withdrawn because of refusal of further treatment for neuropathy after the first cycle. Clinical responses were defined by established criteria.

Results. Thirty-seven patients were included in this intent-to-treat study. The overall clinical response rate was 45.9% (5 complete responses, 12 partial responses). The clinical response rate in patients with measurable tumor was 25.0% (2 complete responses, 1 partial response), while that in patients without measurable tumor and with assessable CA 125 levels was 56.0% (3 complete responses, 11 partial responses). Clinical response rate in patients with chemotherapy-free interval more than 6 months had about twice higher than that in patients with chemotherapy-free interval less than 6 months. The clinical response rate by number of prior regimens revealed that as number of prior regimens increases, the response rate decreases.

Conclusion. Weekly paclitaxel has significant antitumor activity in heavily pretreated patients with recurrent or persistent ovarian carcinoma and warrants as second or third line chemotherapy in such setting.

Keywords: Weekly paclitaxel; Ovarian cancer; Second line chemotherapy; CA 125

Introduction

Ovarian cancer is the fourth leading cause of cancer death in the female population and the most fatal gynecologic malignancy. The disease is surgically curable when localized (stage I to II). However, the majority of patients present, initially and at relapse, with bulky intra-abdominal disease that is not surgically resectable. Systemic cisplatin-based chemotherapy in combination with debulking surgery has become the standard for initial therapy, with reported response rates that range from 50% to 80% [1]. Unfortunately, the majority of patients eventually die of disease persistence or recurrence, with the abdominal cavity being the most common site of recurrence. The management of tumor recurrence remains a clinical challenge, since the

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chance of response to a secondary treatment is currently less than 20% [2], especially if the disease is platinum-resistant [3]. To improve this outcome, several clinical trials are now exploring the possibility of incorporating new drugs into the first-line chemotherapy regimen [4]. Furthermore, new biological agents and molecularly targeted therapies aimed to overcome drug resistance with less toxic effects are under investigation [5].

Paclitaxel, a unique antimicrotubule agent, has been one of the most promising drugs to enter into clinical trials in the setting of cisplatin-refractory ovarian cancer. Responses have been reported in both heavily and minimally pretreated ovarian cancer patients (20% to 37%) [6,7]. However, myelotoxicity was found to be a major concern even with granulocyte colony-stimulating factor (G-CSF) support. In order to minimize toxicity, paclitaxel can be given weekly instead of triweekly [8,9]; this results in a higher dose intensity of the drug [10]. Two non-randomized trials [11,12] have suggested that the activity of paclitaxel in epithelial ovarian cancer is dose-dependent, and a randomized trial [10] has shown reduced toxicity with weekly scheduling without detriment to efficacy. We have reported that single weekly paclitaxel has moderate activity in heavily pretreated ovarian cancer patients, and 80 mg/m^2 of paclitaxel was recommended as the phase II dose for outpatients [13]. When 80 mg/m^2 of paclitaxel was given, the dose intensity may not be greater than every triweekly. However, continuous low-dose paclitaxel so-called metronomic chemotherapy has been reported to result in antiangiogenic effects and tumor dormancy [14,15]. Thus, we attempted to determine effects of single weekly paclitaxel in heavily pretreated patients with recurrent or persistent ovarian cancer.

Patients and methods

Eligibility criteria

Eligible patients had recurrent or persistent ovarian cancer that was histologically proven at primary diagnosis. All patients had either measurable or assessable disease. Disease was classified as measurable if the patient had bidimensionally measurable disease by computed tomography (CT). Assessable disease was only used in patients with no measurable disease and was defined as a CA 125 $\geq$ 75 U/ml. Eligibility criteria required the patients to have a baseline leukocyte count >2500, absolute neutrophil count >1500, platelet count >75000, serum creatinine <1.5 mg/dl, serum bilirubin <2.5 mg/dl, and liver function tests <3 times the laboratory standard value. Patients were required to have a life expectancy of at least 2 months and any Gynecologic Oncology Group (GOG) performance score was acceptable for enrollment in this study. Thirty-seven of 39 patients enrolled were eligible for this study. Twenty-three and 14 patients had chemotherapy-free interval $\geq$6 months and <6 months, respectively. Patients must have had one or more previous chemotherapy regimens (Table 1).

Exclusion criteria included borderline histology, pregnancy, fertility, diagnosis of another malignancy within the past 5 years, prior treatment with weekly paclitaxel, active infection, hepatitis, gastrointestinal bleeding, congestive heart failure, unstable angina, or myocardial infarction in the past 6 months.

Study design

This study was a nonparametric multicenter study of weekly paclitaxel. The investigative sites involved were National Defense Medical College in Saitama and Jichi Medical School in Tochigi, Japan. All investigative sites obtained institutional review board approved and all patients provided signed informed consent.

Treatment plan

Eligible patients who signed informed consent underwent a complete history and physical exam. Pretreatment laboratory tests included a complete blood count (CBC), chemistry panel to include glucose, electrolytes, BUN, creatinine, SGOT, SGPT, bilirubin, alkaline phosphatase, CA 125 level,

Table 1
Patient characteristics

Characteristic	No. of patients	%
Patients		
Enrolled	39	
Eligible	37	
Median age (range)	59 (42–74)	
Original FIGO stage		
Ia	1	2.7
Ic	2	5.4
IIIa	2	5.4
IIIc	23	62.2
IV	9	24.3
Histological type		
Serous	26	70.3
Clear	3	8.1
Mucinous	2	5.4
Endometrioid	2	5.4
Others	4	10.8
Chemotherapy-free interval[a]		
≥6 months	23	62.2
<6 months	14	37.8
Prior regimens		
1	19	51.4
2	14	37.8
3	4	10.8

[a] Interval from prior chemotherapy to start of weekly paclitaxel.

chest X-ray, EKG, and CT scan or magnetic resonance imaging (MRI).

On days 1, 8, and 15 of each 28-day cycle (1 cycle), patients received intravenous infusions of paclitaxel at 80 mg/m^2. Paclitaxel was given as a 1-h intravenous infusion via non-PVC tubing and connectors. Premedications consisted of diphenhydramine (50 mg), cimetidine (300 mg), and dexamethasone (20 mg) intravenously given 30 min before paclitaxel infusion. A minimum of six doses (two cycles) were administered at weekly intervals. Chemotherapy was withheld for white cell counts below 2500/mm^3 or absolute neutrophil counts below 1500/mm^3 and for platelet counts below 75 000 mm^3. Toxicity was assessed by using the GOG scoring system [16]. In patients with progression of disease, chemotherapy was either stopped or changed to another agent. In patients with stable disease or a clinical response, weekly paclitaxel was continued until disease progression or adverse effects necessitated removal from the study. Withdrawal from the study at patient request was allowed at any time.

Response assessment

Although most of the patients had elevated CA 125 levels, many did not have measurable disease on CT, MRI, or clinical exam. Hence, the criteria for response was based on declining CA 125 levels as described by Rustin et al. [17]. Partial response was defined by reduction of CA 125 by more than 50% after two samples or greater than 75% serial reduction over three consecutive samples, with the final sample taken at least 28 days after the previous sample. This has been correlated to standard response criteria as defined by the Gynecologic Oncology Group (GOG) in patients with measurable disease [18]. Partial response by CT scan was defined as a 50% reduction in the sum of the two perpendicular diameters of all measurable tumors for at least 1 month. Complete response was defined as total disappearance of all clinically or radiologically measurable tumors with normalization of CA 125 levels (<35) for at least 1 month. Progression of disease was defined as appearance of new lesions or an increase of more than 50% in the sum of two perpendicular diameters of any existing lesion or increase in CA 125 levels on two consecutive measurements. The term stable disease was used for any response that fell in between progression and a partial response. For statistical comparison, the Mann–Whitney two-sample test and Fisher's Exact Test have been used. Time to progression (TTP) was measured as interval from prior chemotherapy to start of the weekly paclitaxel for progression. Survival was measured from start of the weekly paclitaxel to the date of death or last contact if the date of death is unknown.

Table 2
Clinical response (N = 37 evaluable patients)

Response	No. of patients	%
Complete response	5	13.5
Partial response	12	32.4
Stable disease	16	43.2
Progression	4	10.8

Table 3
Response with tumor regression (N = 12 evaluable patients)

Response	No. of patients	%
Complete response	2	16.7
Partial response	1	8.3
Stable disease	6	50.0
Progression	3	25.0

All patients had morphologically measurable tumor.

Results

From April 1999 to September 2002, 39 patients were enrolled in this prospective trial and received weekly paclitaxel therapy. Two patients were withdrawn because of refusal of further treatment for neuropathy after the first cycle. Demographics for the 37 evaluable patients are listed in Table 1. Twenty-three patients (62.2%) had chemotherapy-free interval ≥6 months. All of 14 (37.8%) patients with chemotherapy-free interval <6 months had platinum-based chemotherapy. The number of patients with one prior chemotherapy regimen was 19, that with two prior regimens was 14, and that with three prior regimens was 4. Primary chemotherapy consisted of 30 patients with combination chemotherapy by cisplatin, Adriamycin, and cyclophosphamide (CAP), 4 patients with combination chemotherapy by paclitaxel and carboplatin (TJ), and 3 patients with combination chemotherapy by carboplatin and cisplatin (JP). Performance status (GOG) of all patients enrolled was 0 or 1.

All 37 patients were evaluable for response. Five patients (13.5%) showed a complete response, 12 (32.4%) showed a partial response. Total response rate was 45.9% (Table 2).

Two (16.7%) out of 12 patients with measurable tumor had complete response and 1 (8.3%) had partial response. The response rate was 25.0% (Table 3). Regarding response based on CA 125 levels, 3 (12.0%) of 25 patients had complete response and 11 (44.0%) had partial response. The

Table 4
Response based on CA 125 levels (N = 25)

Response	No. of patients	%
Complete response	3	12.0
Partial response	11	44.0
Stable disease	10	40.0
Progression	1	4.0

No patient had morphologically measurable tumor.

Table 5
Clinical response according to chemotherapy-free interval ($N = 37$)

	Chemotherapy-free interval			
	<6 months[a]		≥6 months	
Total	14		23	
Response				
Complete	1	7.1%	3	13.0%
Partial	3	21.5%	10	43.5%
Stable	9	64.3%	7	30.5%
Progression	1	7.1%	3	13.0%

[a] All patients received platinum-based chemotherapy.

response rate was 56.0%, showing more than two times of response rate of patients with measurable tumor (Table 4). One (7.1%) of 14 patients with chemotherapy-free interval <6 months had complete response, while 3 (13.0%) of 23 patients with chemotherapy-free interval ≥6 months had complete response. Three patients (21.5%) with chemotherapy-free interval <6 months had partial response, while 10 patients (43.5%) with chemotherapy-free interval ≥6 months had partial response. The response rate (56.5%) of patients with chemotherapy-free interval ≥6 months was about two times higher than that (28.6%) with chemotherapy-free interval <6 months (Table 5). Clinical response rate according to number of prior regimens showed that as number of prior regimens increases, the response rate decreases (Table 6). Median TTP and overall survival were 12 months and 21 months, respectively.

A total of 468 doses (range, 6–39) of weekly paclitaxel were administered to the 37 patients. Toxicity data was available for all the 37 patients. Hematological toxicity more than grade 2 was observed in about 25%, while non-hematological toxicity was observed in 1 (2.7%) of 37 patients (Table 7). Nine patients (24.3%) had a grade 3 or 4 neutropenia. Four patients had treatment delays and two patients required granulocyte colony-stimulating factors intermittently for severe neutropenia, but there were no hospital administrations for neutropenic fever. Four patients had a grade 3 anemia, and two of them required blood transfusion. During treatment with weekly paclitaxel, one patient had a grade 3 neuropathy and the chemotherapy had to be stopped. There was no evidence for cumulative hematological and non-hematological toxicity.

Table 6
Clinical response according to number of prior regimens

	Number of prior regimens					
	1		2		3	
Total	19		14		4[a]	
Response						
Complete	4	21.2%	1	7.1%	0	
Partial	7	36.8%	4	28.6%	1	25.0%
Stable	7	36.8%	7	50.0%	2	50.0%
Progression	1	5.3%	2	14.3%	1	25.0%

[a] All patients with three prior regimens had measurable tumor.

Table 7
Toxicity profiles

Hematological toxicity	No. of patients
Neutropenia	
Grade 3	7
Grade 4	2
Leukopenia	
Grade 3	9
Grade 4	1
Thrombocytopenia	
Grade 3	0
Grade 4	0
Anemia	
Grade 3	4
Grade 4	0
Non-hematological toxicity	**No. of patients**
Peripheral neuropathy	
Grade 2	5
Grade 3	1
Alopecia	
Grade 2	11
Grade 3	0

Discussion

The treatment of recurrent and refractory cancer is a challenging problem because recurrent or refractory disease is almost never curable. The majority of patients who initially respond will develop chemotherapy-resistant disease and ultimately die. Thus, the primary treatment objectives in the salvage setting are prolonging remission and maintaining quality of life. These goals may be attainable through the evaluation of different dosing and timing regimens of standard chemotherapeutic agents.

Introduction of paclitaxel into the armamentarium of drugs to treat platinum-resistant ovarian cancer has been one of the more significant advances in the treatment of ovarian cancer in the last decade. Paclitaxel has a unique mechanism of action, is cell-cycle-specific, and acts by promoting the stability of the microtubule assembly during mitosis. In vitro data suggest that the duration of exposure plays a crucial role in the cytotoxic efficacy of paclitaxel [19,20]. Resistance to paclitaxel-mediated P-glycoprotein (Pgp) [21] has been shown to be significantly reduced by increasing the duration of exposure to paclitaxel from 3 to 96 h in Pgp-expressing paclitaxel-resistant breast cancer cell lines [22].

Weekly administration of paclitaxel has the potential to have an effect similar to that of continuous infusion while

taking advantage of the minimal hematological toxicity associated with shorter infusions. Neutropenia was the most frequent hematological adverse event observed in patients receiving once-weekly intravenous paclitaxel monotherapy. Severe neutropenia was dose-related, occurring in 3% and 15% of patients receiving 80 mg/m^2 monotherapy [23,24]. An absolute neutropenia count of 1000 has been shown to be sufficient for dosing weekly paclitaxel on any given scheduled day of treatment. In the present study, severe neutropenia and leukopenia of grade 4 were observed in 2 (5.4%) and 1 (2.7%) of 37 patients. Other hematological adverse events (grade 4 anemia or grade thrombocytopenia) were not observed. Neuropathy is experienced by most patients receiving once-weekly intravenous paclitaxel monotherapy and is usually mild or moderate [23,24]. The incidence of severe neuropathy with paclitaxel 80 mg/m^2 once weekly was approximately 10% [23,24]. Most patients experienced mild myalgia and/or arthralgia; few patients reported severe symptoms [25]. In the present study, 3/39 (7.7%) containing two patients withdrawn from this trial experienced severe neuropathy. Although alopecia of grade 2 was observed in 11/37 (29.7%), alopecia beyond grade 2 was not observed (Table 7). No patient required dose reduction was observed in this trial. Prolonged exposure to relatively low concentrations of paclitaxel has been shown to induce apoptosis [26]. In addition, prolonged low-dose paclitaxel exposure has been reported to have anti-angiogenic properties [27]. The paclitaxel dose delivered in this regimen is 24 mg/m^2 over 3 weeks as compared to 175 mg/m^2 every 3 weeks with conventional dosing. These features associated with weekly low-dose paclitaxel may explain the response seen in patients with carcinoma refractory to conventionally dosed paclitaxel.

Fennelly et al. [8] did a phase I trial with 18 patients with platinum- and paclitaxel-resistant ovarian cancer and determined that 80 mg/m^2 was the maximally tolerated dose. We also reported in the phase I study that the same dose of 80 mg/m^2 was the maximum recommended dose [13]. Thus, we performed phase II study by single weekly 80 mg/m^2 paclitaxel. Treatment with single weekly 80 mg/m^2 paclitaxel brought about an overall response rate of 45.9%, similar to that of a recent report [28]. It is noteworthy that five complete responses among 37 patients with one or more therapeutic regimens were achieved (Table 2). In addition, 3 (25.0%) of 12 patients with measurable tumor containing two complete responses had response to weekly paclitaxel (Table 3). When based on CA 125 levels, the response rate of 56.0% including a complete response of 12.0% was obtained, showing two times higher response rate compared to that in patients with measurable tumor (Table 4). These results suggest that patients with recurrence detectable only by CA 125 levels (but not morphologically measurable) are more sensible to weekly paclitaxel than those with measurable tumor. It is possible that angiogenesis of detectable tumor only by CA 125 is vulnerable to weekly paclitaxel than that of morphologically measurable tumor. Response rate (56%) of patients with chemotherapy-free interval ≥6 months showed about two times that (28.6%) of those with chemotherapy-free interval <6 months (Table 5). Similarly, a recent report demonstrated that all the responders with paclitaxel-resistant tumors were seen in patients with a paclitaxel-free interval of more than 12 months [28]. Since most of prior regimens used in patients enrolled in the present study were cisplatin-based chemotherapy, weekly paclitaxel seemed to be more effective in patients with longer platinum-free interval. In addition, we examined clinical response according to number of prior regimens. When prior regimen was 1 or 2, the clinical response rate was 58.0% or 35.7%, respectively, whereas in patients with three prior regimens, the responder was only one (25.0%) (Table 6). These results suggest that as number of prior regimens increases, the response rate decreases and therefore patients with less prior regimens may have better be treated with weekly paclitaxel. It is noteworthy that 9 of 14 patients with two prior regimens received chemotherapy containing paclitaxel while all patients with three prior regimens received chemotherapy containing paclitaxel. However, efficacy of weekly paclitaxel was not influenced by kinds of prior chemotherapy regimen.

The choice of second line drug in this present setting is dependent on toxicity and quality of life considerations, in addition to efficacy. Weekly administration of paclitaxel by 1-h infusion has been reported to have less toxicity than other schedules and primary effect in patients with pretreated gynecologic cancers [8,10,29,30]. In addition, a randomized trial comparing the weekly schedules to tri-weekly paclitaxel for advanced breast cancer is nearing completing in the GALGB. 'Metronomic' dosing or anti-angiogenic scheduling of cancer chemotherapeutics has been increasingly recognized to be a potential application of paclitaxel in cancer therapy [31–33].

In conclusion, weekly low-dose paclitaxel used in the present study is considered safe and effective in pretreated patients with recurrent or persistent ovarian cancer. Encouraging response rates in both platinum-sensitive and platinum-resistant patients warrant further studies.

References

[1] Silverberg E, Boring C. Cancer statistics 1990. CA Cancer J Clin 1990;40:9–26.
[2] Colombo N, Parma G, Bocciolone L, Sider M, Franchi D, Maggioni A. Role of chemotherapy in relapsed ovarian cancer. Crit Rev Oncol Hematol 1999;32:221–8.
[3] 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;9:389–93.
[4] Bookman M. Developmental chemotherapy in ovarian cancer: incorporation of newer cytotoxic agents in a phase III randomized trial of the Gynecologic Oncology Group (GOG-0182). Semin Oncol 2002; 29(S1):30–1.
[5] Ozols RF. Future directions in the treatment of ovarian cancer. Semin Oncol 2002;29(S1):32–42.

[6] McGuire WP, Rowinsky EK, Rosenshein NB, et al. Taxol: a unique antineoplastic agent with significant activity in advanced epithelial ovarian neoplasms. Ann Intern Med 1989;111:273–9.
[7] Sarosy G, Kohn E, Link C, et al. Taxol dose intensification in patients with recurrent ovarian cancer. Proc Am Soc Clin Oncol [abstr.] 1992;11:226.
[8] Fennelly D, Aghajanian C, Shapiro F, O'Flaherty C, McKenzie M, O'Connor C, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 1997;15:187–92.
[9] Seidman AD, Hudis CA, Albanel J, et al. Dose dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 1998;16:3353–61.
[10] Anderson H, Boman K, Ridderheim M, et al. Updated analysis of a randomized study of single agent paclitaxel given weekly vs 3 weeks to patients with ovarian cancer treated with prior platinum therapy. Proc Am Soc Clin Oncol [abstr 1505] 2000;19:380a.
[11] Kohn EC, Sarosy G, Bicher A, et al. Dose-intense Taxol: high response rate in patients with platinum-resistant recurrent ovarian cancer. J Natl Cancer Inst 1994;86:18–24.
[12] Kohn EC, Sarosy GA, Davis P, et al. A phase I/II study of dose-intense paclitaxel with cisplatin and cyclophosphamide as initial therapy of poor-prognosis advanced-stage epithelial ovarian cancer. Gynecol Oncol 1996;62:181–91.
[13] Takano M, Kikuchi Y, Kita T, Suzuki M, Ohwada M, Yamamoto T, et al. Phase I and pharmacological study of single paclitaxel administered weekly for heavily pretreated patients with epithelial ovarian cancer. Anticancer Res 2002;22:1833–8.
[14] Miller KD, Sweeney CJ, Sledge Jr GW. Redefining the target: chemotherapeutics as antiangiogenics. J Clin Oncol 2001;19:1195–206.
[15] Kerbel RS, Klement G, Pritchard KI, Kamen B. Continuous low-dose anti-angiogenic/metronomic chemotherapy: from the research laboratory into the oncology clinic. Ann Oncol 2002;13:12–5.
[16] Blessing A. Design, analysis and interpretation of chemotherapy trials in gynecologic cancer. In: Deppe G, editors. Chemotherapy of Gynecologic Cancer, second ed. New York, NY: Alan R. Liss, Inc., Scientific and Medical Publications; 1990. p. 63–97.
[17] Rustin GJS, Nelstrop AE, McClean P, Brady MF, McGuire WP, Hoskins WJ, et al. Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. J Clin Oncol 1996; 14:1545–51.
[18] Markman M, Hoskins W. Responses to salvage chemotherapy in ovarian cancer: a critical need for precise definitions of the treated populations. J Clin Oncol 1992;10:513–4.
[19] Lopes NM, Adams EF, Pitts TW, Bhuyan BK. Cell kill kinetics and cell cycles effects of Taxol on human and hamster ovarian cell lines. Cancer Chemother Pharmacol 1993;432:235–42.
[20] Georgiadis MS, Russell E, Gazdar AF, Johnson BE. Paclitaxel cytotoxicity against human lung cancer cell lines increases with prolonged exposure duration. Clin Cancer Res 1997;3:449–54.
[21] Yamamoto K, Kikuchi Y, Kudoh K, Nagata I. Modulation of cisplatin sensitivity by Taxol in cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. J Cancer Res Clin Oncol 2000;126:168–72.
[22] Zhan Z, Scala S, Monks A, Hose C, Bates S, Fojo T. Resistance to paclitaxel mediated by P-glycoprotein can be modulated by changes with schedule of administration. Cancer Chemother Pharmacol 1997;40:245–50.
[23] Perez EA, Vogel CL, Irwin DH, et al. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol. 2001;19:4216–23.
[24] Socinski MA, Schell MJ, Bakri K, et al. Second-line, low-dose, weekly paclitaxel in patients with stage IIIB/IV non-small cell ling carcinoma who fail first-line chemotherapy with carboplatin plus paclitaxel. Cancer 2002;95:1265–73.
[25] Kikuchi Y, Hiramatsu H, Seto H, Kita T. A rare case of advanced ovarian carcinoma who developed difficulty walking 25 days after treatment with weekly paclitaxel. Anti-Cancer Drugs 2001;12:631–3.
[26] Saunders DE, Lawrence WD, Christensen C, Wappler NL, Ruan H, Deppe G. Paclitaxel induced apoptosis in MCF-7 breast cancer cells. Int J Cancer 1997;70:214–20.
[27] Klanber N, Parangi S, Flynn E, Hamel E, D'Anato RJ. Inhibition of angiogenesis and breast cancer in mice by the microtubule inhibitors 2-methylestradiol and Taxol. Cancer Res 1997;57:81–6.
[28] Ghamande S, Lele S, Marchetti D, Baker T, Odunsi K. Weekly paclitaxel in patients with recurrent or persistent advanced ovarian cancer. Int J Gynecol Cancer 2003;13:142–7.
[29] Abu-rustum N, Aghajanian C, Barakat RR, et al. Salvage weekly paclitaxel in recurrent ovarian cancer. Semin Oncol 1997;24(S15):62–7.
[30] Klaasen V, Wilhe H, Strumberg D, et al. Phase I study with a weekly 1 h infusion of paclitaxel in heavily pretreated patients with metastatic breast and ovarian cancer. Eur J Cancer 1996;32A:547–9.
[31] Kerbel RS. Tumor angiogenesis: past, present, and the near future. Carcinogenesis 2000;21:505–15.
[32] Schimer M. Angiogenic chemotherapeutic agents. Cancer Metast Rev 2000;19:67–73.
[33] Wang J, Lou P, Lesniewski R, Henkin J. Paclitaxel at ultra low concentrations inhibits angiogenesis without affecting cellular microtubule assembly. Anti-Cancer Drugs 2000;14:13–9.

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プロトコールコンセプト

III/IV 期卵巣癌、卵管癌、腹膜癌に対する
化学療法先行治療と手術先行治療
のランダム化比較試験

略称：OVCA-NAC-P3

試験タイプ：Phase III

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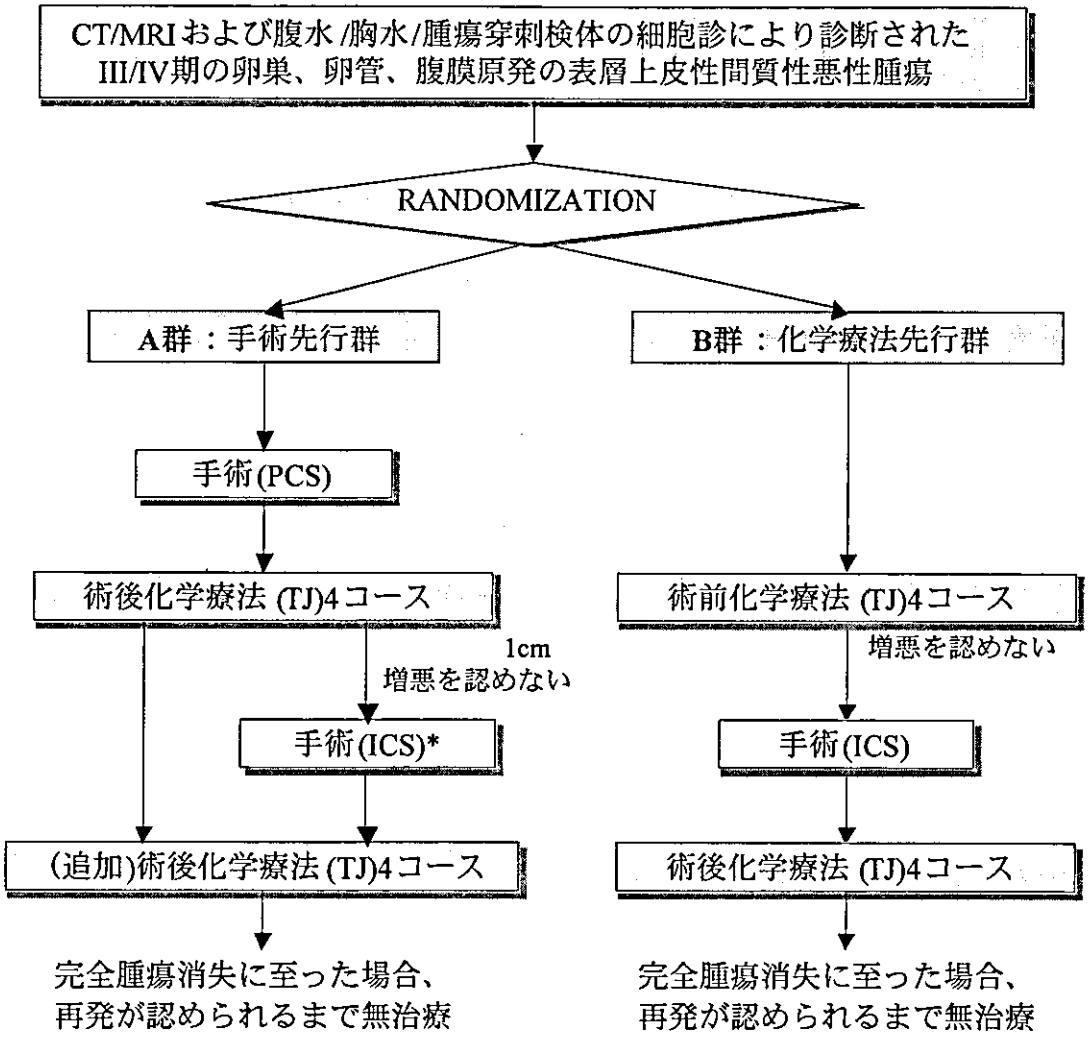
0. 本試験のシェーマ



*手術先行群の PCSで残存腫瘍 ≧cmの場合、術後化学療法にて増悪を認めなければ、化学療法4コース後、 ICS施行可。

1. 目的とエンドポイント

1-1. 目的

卵巣癌、卵管癌、腹膜癌の進行症例の予後改善を目的として、化学療法を先行して手術を行なう治療法の有用性を、卵巣癌、卵管癌、腹膜癌に対する標準治療である手術を先行して化学療法を行なう治療法とのランダム化比較において評価し、卵巣癌、卵管癌、腹膜癌の進行症例に対する標準的治療法を確立する。

1-2. Primary endpoint 生存期間

1-3. Secondary endpoint 完全腫瘍消失割合*、無増悪生存期間、薬物有害反応、手術合併症割合、開腹手術回数、総開腹手術時間、周術期輸血量、周術期血漿製剤使用量

*:完全腫瘍消失とは CT または MRI で全ての病変が消失し、胸部 XP にて胸水の貯留を認めず、CA125<20U/ml となった状態と定義する。

2. 背景

2-1. 卵巣癌の疫学・予後

我が国における卵巣癌は、欧米に比べその頻度は少ないものの、発症頻度は年々増加傾向にあり、年齢調整罹患率は 1975 年の 4.5 人から 1998 年には 8.3 人に増加し、1998 年には 6,742 人が新たに卵巣癌と診断された。また卵巣癌は婦人科性器癌の中で最も予後不良であり、2001 年の統計では、婦人科性器癌の中で最も多く、女性死亡数の 3.48%にあたる、4,154 人が卵巣癌のため死亡している。その原因として、卵巣癌は、症状が出にくく、また適当な検診法もないため、診断がついた時点では多くの症例がすでに進行した状態であることが挙げられる(Stage III/IV 症例は全体の約 60%)。上皮性卵巣癌(胚細胞腫瘍や性索間質性腫瘍などを除いたもので卵巣癌の 90%を占める）の治療成績は化学療法の改善により、奏効率、生存率ともに向上したものの、骨盤外の腹腔内進展、後腹膜リンパ節転移、遠隔転移のいずれかがある進行卵巣癌(III/IV 期)では 3 年生存率 25%、5 年生存率で約 20%しかない。

2-2. 進行卵巣癌に対する標準治療

III/IV 期卵巣癌に対する治療は、手術療法と化学療法の組み合わせであり、現在の標準治療は、最初に開腹手術を行い、術後に化学療法を行なう方法である(手術先行)。遠隔転移を伴う IV 期でも、遠隔転移が明らかに腹腔内腫瘍よりも短期的生命予後に関連する場合や PS4 の場合を除き、開腹手術を先行させるのが標準治療である。

最初に行なう開腹手術の目的は、卵巣癌であることを腫瘍の局在と組織学的所見により確認し、進行期を正確に診断することである(staging laparotomy)。進行卵巣癌の場合には、可能な限り転移病巣を切除して腫瘍を縮小することも同時に行われ、初回腫瘍縮小(減量）手術(primary cytoreductive surgery：PCS)と呼ばれる。これらの目的のために行われる術式は、子宮、卵巣、卵管、大網の切除および転移病巣の局在に応じて直腸低位前方切除、結腸切除、小腸切除、脾摘、腹膜切除、虫垂切除、骨盤および傍大動脈リンパ節郭清術などである。1975 年に Griffiths が、初回手術後の最大残存腫瘍径が進行卵巣癌の予後と関連することを報告して以来、多くの報告によりその関連が確認され、不完全切除であっても広汎で侵襲的な腫瘍縮小手術を行なう根拠となっている。PCS の目標は、optimal surgery(最大残存腫瘍径が 2cm 未満あるいは 1cm 未満、3cm 未満など種々の定義が用いられているが、本試験では 1cm 未満を採用)である。

卵巣癌に対する化学療法としては、Cisplatin(CDDP)、Carboplatin(CBDCA)などの白金製剤と Paclitaxel(PTX)、Docetaxel(DOC)などのタキサン系薬剤の 2 剤併用療法が主として行われており、現時点では PTX(175-185mg/m^2、3 時間投与)と CBDCA(AUC 5-6)の併用療法(TJ 療法)を 3 週ごとに 6-9 コース行なうことが進行卵巣癌に対する標準化学療法とされている。TJ 療法の卵巣癌初回治療における有効性に関して、phase I-II 試験の結果、奏効率は 70-100%、完全奏効率は 24-83%と良好な成績が報告されている。

進行卵巣癌(III/IV 期)に対する手術先行の標準治療の問題点として、

1) 術前に PS4 の症例を除いたとしても、術中に起こる腹水産生や胸水産生に伴う呼吸循環不全や出血傾向のため、侵襲の大きな腫瘍縮小手術(PCS)は行なうことのできない症例が、少なくない。

2) 治療関連死を含む重篤な合併症が比較的高率(最大で 7%の報告)に認められる。

3) 初回の腫瘍縮小手術により、optimal surgery が達成できるのは、一般には 40%程度の症例に限られ、suboptimal(最大残存腫瘍径が optimal surgery の定義を越える大きさとなった場合)の症例においては、初回化学療法中に第 2 回目の腫瘍縮小手術が必要となることが多い。つまり、2 度の大きな開腹手術を行なう症例が少なくなく、患者にとって大きな負担である。

4) 初回手術に optimal surgery を想定した場合、予定手術時間は 5-6 時間以上の枠を必要とするため、初診から手術まで 4 週間以上要する施設が多い。術後約 2 週間で化学療法を開始することが多いが、初診から化学療法開始まで 6 週間以上を要することになる。

などが挙げられる。

2-3. 卵巣癌における Neoadjuvant chemotherapy

化学療法の進歩による奏効率の向上とあいまって、近年進行卵巣癌に対する化学療法先行治療、つまり neoadjuvant chemotherapy(NAC)に期待が持たれるようになった。NAC には次の利点がある。

1) 早い時期に(初診から 2-3 週間以内に) 全身的化学療法を開始できる。

2) PS の改善、腫瘍の縮小、胸水・腹水の減量により、より安全な状態で腫瘍縮小手術を行ないうる。

3) 他臓器合併切除の頻度が減少し、腫瘍縮小手術自体が施行しやすくなる。

4) 術式を拡大しなくても optimal surgery が達成できる可能性や根治性の高い手術の可能性が高くなる。

5) 腫瘍縮小手術は初回治療中には 1 回のみである。

以上のように、NAC 療法によって進行卵巣癌の治療成績の改善が期待され、また、同時に術後の重篤な合併症や他臓器合併切除の減少から、患者の QOL(quality of life)の改善も期待される。

起こりうる欠点としては、次のことが考えられる。

1) 開腹手術先行に比べ、原発診断/進行期診断/組織診断において、不正確になる危険性がある。

2) 化学療法に不応(PD)の場合、手術不能となる可能性がある。

3) 化学療法後の腫瘍縮小手術(interval cytoreductive surgery：ICS)において、肉眼的所見から切除範囲を縮小しすぎる可能性がある。

などである。

2-4. NAC 療法と標準治療の比較成績

これまで報告されている進行卵巣癌における NAC 療法と標準治療を比較した報告はいくつか認められるが、現在までの報告は Kuhn らの non-randomized 第 II 相比較試験の報告以外はいずれも retrospective study である。

Jacob らは、PCS にて生検のみの試験開腹に終わり他院より紹介された患者に対して、NAC 療法を行なった 22 例とすぐに再度腫瘍縮小手術を行なった標準治療群 18 例を比較し、生存率には

有意差は認められなかったものの、NAC 群において有意に optimal surgery の割合が高かったことを報告している(77% vs. 39%)。

Onnis らの報告では、胸水/肝転移/腸管播種の有無などにより NAC 群を決定、88 例に対して NAC 療法を行ない、標準治療を行った 284 例と比較した。腫瘍縮小手術において、NAC 療法群においてより高率に optimal surgery が可能であった(42% vs. 29%)。また NAC 群では、より進行し全身状態不良の症例が多いものの、3 年、5 年生存率に差は認められなかった。

Schwartz らは、全身状態/合併症により手術不能な症例、画像診断(CT)により腫瘍切除不能と評価した 59 例に NAC 療法を施行、標準治療を行った 206 例と比較した。NAC 療法群では、標準治療群に比較して、有意に高齢で PS 不良であったが、生存率に有意な差は認められなかった。腫瘍縮小手術の比較においては、NAC 療法群で出血量、ICU 滞在日数、入院日数などが有意に標準治療群に比して少なかったと報告している。

Vergote らは、進行卵巣癌症例を対象として、切除可能性を試験開腹あるいは腹腔鏡により判断し、切除可能例には標準治療、不能例には NAC 療法を行なうという方針で治療を行なった 1989-1997 年の治療成績を、NAC 療法導入以前の、全例に標準治療を行なうという治療方針で治療を行なった 1980-1988 年の治療成績と比較し、NAC 療法導入後の方が全体として予後良好(3 年生存率、42% vs. 26%)であったと報告している。時代により、化学療法剤や手術手技などにも違いはあると考えられるが、NAC 療法の有用性を示す結果といえる。

Kayikçio_lu らは、胸水貯留例、肝転移例、切除不能が予想される多発転移症例や全身状態不良例 45 例に NAC 療法を行い、標準治療を行った 158 例と比較した。腫瘍縮小手術において、結腸切除や脾摘を要した割合は NAC 群において有意に低かったが、肉眼的完全切除は NAC 群でより高率に達成された(49% vs. 14%)。NAC 療法群では、標準治療群に比べて、有意に高齢で PS 不良であったが、両者の間に 5 年生存率および MST で有意差は認められなかった。

Kuhn らは、多量の腹水貯留(>500ml)を認める進行卵巣癌症例を対象に NAC 療法(31 例)と標準治療(32 例)の non-randomized の第二相比較試験を行った。NAC 療法群では標準療法群に比して、高率に optimal surgery が達成でき(84% vs. 63%)、MST の延長を認めた(42M vs. 23M)と報告している。

これまでの報告で、NAC 療法群が標準治療群に予後において優っているという報告は、Kuhn らの報告のみであるが、その他の報告でも、少なくとも劣っているという結果は認められない。しかも、Onnis ら、Schwartz ら、Kayikçio_lu らの報告では、初回に腫瘍縮小手術が不能、あるいは全身状態のため手術不能で、結果的に術前化学療法となった症例を NAC 療法群として標準治療群と比較した結果である。NAC 療法は、進行卵巣癌に対する新たな標準治療として、検討に値する治療と考えられる。

2-5. 現在進行中の比較試験

Retrospective study の結果を踏まえて、EORTC(European Organization for Research and Treatment of Cancer)の Vergote らは、第 III 相比較試験として EORTC55971 を開始した。卵巣癌(+卵管癌・腹膜癌)IIIC/IV 期を対象に、診断的腹腔鏡、試験開腹、穿刺組織診のいずれかの方法で原発診断、

組織診断、進行期診断の後、化学療法先行群(NAC 群)と手術先行群に randomize している。卵管癌・腹膜癌は、組織学的所見、化学療法感受性、予後が卵巣癌とほぼ同一であり、卵巣・卵管の摘出なしでは鑑別診断困難であることから対象に含めている。プロトコール治療は、NAC 群および suboptimal surgery に終わった手術先行症例では、3 コースの化学療法の後、腫瘍縮小手術(ICS)を行い、術後 3 コースの化学療法の追加、optimal surgery が達成された手術先行症例では、術後 6 コースの化学療法である。化学療法としては、参加施設の実状にあわせてプラチナ製剤(CDDP or CBDCA)+タキサン系薬剤(TXL or DOC)のいずれの組み合わせでも可としている。この臨床試験は 1998 年 9 月から、704 例の登録予定で開始されたが、現在まだ症例登録中である。なお、手術先行群での ICS は後述する GOG152 の結果により、最近 option に変更されている。

2-6. PCS 後の ICS について

EORTC(European Organization for Research and Treatment of Cancer)は、ランダム化比較試験により、初回手術終了時に、最大径 1cm を越える残存腫瘍を有する症例(suboptimal surgery 例）を対象とし、ICS が進行卵巣癌治療において有用であることを示した。つまり、ICS を受けた患者が ICS を受けなかった患者よりも予後が良好であることを示したのである。無増悪生存期間および生存期間は有意に延長し(P=0.01)、生存期間中央値は 6 ヶ月延長した。この試験では、対象症例は、3 コースの CP(CPA/CDDP)療法を受けた後、ICS 施行群と ICS 非施行群に割付けられ、両群ともに CP は計 6 コース行われた。ICS を受けた患者 140 例、ICS を受けなかった患者 138 例が解析された。しかし、最近 GOG152 で同様の症例を対象として、ランダム化比較試験(化学療法は TJ)が行われたが、この試験では ICS の有用性は認められなかった。EORTC では GOG152 に比べて、最大残存腫瘍径が 5cm を越える症例が多かったこと、婦人科腫瘍専門医以外(一般婦人科医や一般外科医）が手術していることが多く手術の quality が低かったこと、化学療法が TJ ではなく CP であったことがこの結果の差であると解釈されている。ICS の有用性には残存腫瘍径が関係していると推測され、大きな残存腫瘍のある症例には、ICS が有用である可能性は否定されていない。従って、本試験では、手術先行の A 群では、PCS 後 1cm 以上の残存腫瘍を認める場合、術後化学療法 4 コース後に ICS を行なうことを可とした(必須ではない)。化学療法先行の B 群では ICS は必須である。

2-7. NAC 療法の feasibility study

厚生労働科学研究費による「進行卵巣癌の予後改善を目指した集学的治療の研究」班(主任研究者：筑波大学産婦人科、吉川裕之)では、厚生労働省がん研究助成金 14 指-4「多施設共同研究の質の向上のための研究体制確立に関する研究」班(主任研究者：国立がんセンターがん予防・検診研究センター情報研究部、福田治彦)との共同研究による JCOG(Japan Clinical Oncology Group)試験として、2003 年 1 月 14 日から、JCOG0206「III/IV 期卵巣癌、卵管癌、腹膜癌に対する術前化学療法の Feasibility study」を行った。本試験の目的は、術前/術後化学療法と腫瘍縮小手術からなる治療法(化学療法先行治療)が、第 III 相の試験治療として適切かどうかを判断し、かつ第 III 相試験を行なう場合、化学療法先行群において診断的腹腔鏡が必須かどうかを決定することであった。

化学療法としては、世界的に標準として用いられているTXLとCBDCAの組み合わせで、術前(NAC)4コース、術後4コースのあわせて8コースの化学療法を行った。対象疾患は、卵管癌・腹膜癌が、組織学的所見、化学療法感受性、予後が卵巣癌とほぼ同一であり、卵巣・卵管の摘出なしでは鑑別診断困難であることから、EORTCのstudyと同様に卵巣癌、卵管癌、腹膜癌とした。

JCOG0206試験の結果、major secondary endpointである正診割合は94.6%(53/56)で、90%以上の正診率を担保する53例以上という条件を満たし、同試験の適格規準を満たす症例においては、第III相試験において診断のための腹腔鏡を省略しうると判断された。正診でなかった点は、3例ともI/II期であったことであるが、うち1例は開腹してIII期であることが判明している。原発診断は全56例が正診であった。また、primary endpointである完全腫瘍消失割合は、腹腔鏡にて正診が確認された53例のうち、プロトコール治療が終了し、CRFが回収された50例中すでに18例で完全腫瘍消失が確認され、「(NAC療法の)真の完全腫瘍消失割合が、無効と判断する閾値割合(20%)以下である」という帰無仮説を棄却するに足る有効症例数(正診例53例の場合、17例)を満たしているため、NAC療法は第III相の試験治療として適切と判断された。

3. 対象症例

3-1. 適格規準

1) 上腹部～骨盤の画像(CTまたはMRI)所見により、卵巣、卵管、腹膜いずれかの原発の悪性腫瘍と診断される。

2) 腹水、胸水または腫瘍穿刺検体の細胞診所見により、卵巣の表層上皮性間質性の悪性腫瘍に相当する組織型が推定される。

3) 上腹部～骨盤の画像(上記のもの)、胸部のXP/CTおよびシンチグラムなどの画像所見により、あるいは細胞診で癌性胸水を証明することにより、進行期III期またはIV期と診断し得る。

4) PCSの対象となりうる。(脳転移、骨髄転移、骨転移のある場合は対象外とする。また、PCSでoptimal debulkingが可能かどうかは問わない。)

5) CA125>200U/mlかつCEA<20ng/ml

6) 初回治療例。(当該疾患に対して、手術、化学療法、放射線療法の既往がなく、他の悪性腫瘍などに対しても化学療法、放射線療法の既往のない症例。)

7) 年令：20才以上75才以下

8) PS (ECOG) 0-3

9) 以下にあげる諸臓器機能が保たれている。(登録前14日以内の最新の検査による。)

- 骨髄機能　WBC≧4,000/mm^3、ANC(好中球：分節核球+桿状核球)≧2,000/mm^3
  Plt≧100,000/mm^3
- 肝機能　AST(GOT)≦60 IU/L、ALT(GPT)≦60 IU/L、Total serum bilirubin≦1.5 mg/dl
- 腎機能　Calculated creatinine clearance≧50 ml/min

$$Ccr(ml/分) = 0.85 \times \frac{(140\text{-}Age) \times Body\ Weight(Kg)}{72 \times Serum\ Cr}$$

- 心機能　正常または治療を必要としない程度の心電図変化

・ 呼吸機能　　血液ガスにて $PaO_2 \geqq 70$

胸水貯留例では、胸水穿刺を行った上で測定して良い。

10) 本人より文書による同意(インフォームド・コンセント)が得られた症例

4. プロトコール治療

4-1. 治療計画

4-1-1. A 群(手術先行群)

登録後、4 週間以内に腫瘍縮小手術(PCS)を行なう。PCS 後 3 週間以内に、術後化学療法を開始する。PCS にて、optimal surgery(残存腫瘍の最大径が 1cm 未満の手術)が達成できた症例では、術後化学療法を 8 コース行なう。PCS にて optimal surgery が達成できなかった場合(suboptimal surgery)は、術後化学療法 4 コース後までに増悪が認められず、かつ腫瘍縮小手術可能な全身状態(PS2 以下など別に定める条件を満たす状態)と判断されれば、術後化学療法 4 コース後 4-7 週間で手術(ICS)を行なうことが出来る。ICS を行なうかどうかの判断は、通常の診療どおり各施設の判断に委ねるが、PCS で optimal surgery の場合は行なわない。ICS が終了してから 3 週間以内に追加術後化学療法を開始する。追加術後化学療法は 4 コース行い、PCS 後の術後化学療法と合わせて化学療法は 8 コース行なう。

4-1-2. B 群(化学療法先行群)

登録後、2 週間以内に術前化学療法を開始する。術前化学療法 4 コース後までに増悪が認められず、かつ腫瘍縮小手術可能な全身状態と判断されれば、術前化学療法 4 コース後 4-7 週間で手術(ICS)を行なう。ICS 可能か否かの判断には optimal surgery が可能と見込まれることを条件としない。ICS が終了してから 3 週間以内に術後化学療法を開始する。術後化学療法は 4 コース行い、術前化学療法と合わせて化学療法は 8 コース行なう。

4-2. 化学療法

Paclitaxel と Carboplatin の併用療法(以下、TJ 療法と略す)を 3 週 1 コースとして行なう。

Paclitaxel($175mg/m^2$)と Carboplatin(AUC 6)は、いずれも day 1 に投与する。Paclitaxel は 3h の点滴静注とし、続いて Carboplatin の点滴静注を行なう。

1) Paclitaxel(TXL)に関して

TXL の投与量の計算に用いる体表面積は、第 1-4 コースは登録時の体重、第 5-8 コースは第 5 コース開始前の体重をもとに算出し、投与量は 5mg 単位で切り捨てて決定する。それ以外の時期での、体重変化に伴う投与量の変更は行なわない。毒性による減量規定は別に設ける。

アナフィラキシー様反応の発現予防のため、TXL 投与前に、デキサメタゾン(デカドロン®)、ジフェンヒドラミン(レスタミン®)およびラニチジン(ザンタック®)による前投薬を行なう。

2) Carboplatin(CBDCA)に関して

CBDCA の投与量の計算は、下記の Calvert の式に従い、10mg 単位で切り捨てて投与量を決定する。GFR として、第 1-4 コースは登録時の体重、第 5-8 コースは第 5 コース開始前の体重および血清クレアチニンをもとに下記の Cockcroft-Gault の式で計算したクレアチニン・クリアランスを用いる。それ以外の時期での、GFR の変化に伴う投与量の変更は行なわない。毒性による減量

規定は別に設ける。日本人の GFR の正常値は、70-130ml/分とされていることから、クレアチニン・クリアランスの計算において、130ml/分を越える値が出た場合、GFR は 130ml/分として、CBDCA の投与量の計算に用いる。(CBDCA の最大投与量は 930mg/body となる。)

Calvert の式

CBDCA(mg) = 目標とする AUC(mg/ml・分) × (GFR(ml/分) + 25)

Cockcroft-Gault の式

$$Ccr(ml/分) = 0.85 \times \frac{(140\text{-}Age) \times Body\ Weight(Kg)}{72 \times Serum\ Cr}$$

4-3. 手術療法

PCS、ICS とも、optimal surgery を目指し、基本手術(子宮全摘術＋両側付属器切除術＋部分大網切除術)施行に加え、可能な限り転移巣も切除する。転移巣の切除には、直腸低位前方切除、結腸切除、脾摘、腹膜切除、虫垂切除、全大網切除、骨盤および傍大動脈(腹部大動脈周囲)リンパ節郭清、などを積極的に行なうこととし、特にその術式に制限を設けず、全身状態の許す範囲で、可及的な腫瘍縮小(減量)手術を行なう。さらに、必要に応じて、腹腔内臓器以外の腫瘍摘出も行なうなど、腹腔内のみならず全身の残存腫瘍径の縮小化に努める。本試験では、残存腫瘍の最大径が<1cm であれば optimal surgery、≥1cm であれば suboptimal surgery と定義する。

4-4. プロトコール治療完了・中止基準

4-4-1. プロトコール治療完了

手術先行群(PCS 群)では、ICS の有無に関わらず、PCS 後に TJ8 コースを完遂した時点で、プロトコール治療完了とする。

化学療法先行群(NAC 群)では、術前化学療法 TJ 4 コース、手術(ICS)、術後化学療法 TJ 4 コースを完遂した時点でプロトコール治療完了とする。

4-4-2. プロトコール治療中止

以下のいずれかに該当する場合、プロトコール治療中止とする

1) 原病の悪化もしくは再発が認められた場合。
- 術前化学療法で PD と判定された場合。
- プロトコール治療期間中に原病の悪化が認められた場合。

2) 毒性(有害事象)によりプロトコール治療が継続できない場合。
- 化学療法により、CTCAE ver3.0 による Grade 3 の神経障害(感覚性)、アレルギー反応/過敏症もしくは Grade 4 の非血液毒性が認められた場合。
- 化学療法のコース開始規準が期間内に満たされなかった場合。
- TXL あるいは TXL と CBDCA が、-3 レベルに減量後も減量規準に合致する毒性が認められた場合。

3) 毒性(有害事象)を理由として、患者がプロトコール治療中止を申し出た場合、あるいは同意の撤回があった場合。

- 毒性との関連が否定できない場合はこの分類を用いる。
- 予定日に来院せず以後患者と連絡が取れないような場合も、毒性との関連が否定できなければこの分類を用いる。

4) 毒性(有害事象)以外の理由で、患者がプロトコール治療中止を申し出た場合、あるいは同意の撤回があった場合。

- 本人や家人の転居等、毒性との関連がまず否定できる場合のみこの分類を用いる。

5) プロトコール治療期間中の患者の死亡。

- 他の理由によりプロトコール治療中止と判断する以前の死亡
- プロトコール治療との関連を問わず、すべての死亡が含まれる。

6) その他

- PCS、および ICS 時に、原発診断、組織学的診断のいずれかにおいて、正診ではないと判断された場合、プロトコール違反が判明した場合など。
- PCS、および ICS が所定の期間内に行われなかった場合。
- 術前、術後の化学療法が所定の期間内に行われなかった場合。
- その他のプロトコール治療中止の場合、治療終了報告用紙のコメント欄に状況を記載する。

プロトコール治療中止日は、5)の場合死亡日、それ以外の場合はプロトコール治療中止と判断した日とする。

4-5. 後治療

プロトコール治療完了後、完全腫瘍消失に至った場合、再発を認めるまで無治療で経過観察する。プロトコール治療中止後の治療、および完了後完全腫瘍消失に至らない場合や、再発後の治療は規定しない。

5. 効果判定の方法と判定基準

5-1. 判定の時期

PCS 群、NAC 群とも化学療法 1 コース毎に化学療法の効果判定を行なう(画像診断での効果判定は 2 コース毎で可とする)。

5-2. 評価方法

化学療法の効果判定には、画像診断(CT/MRI および胸部 XP)、腫瘍マーカー(CA125)、臨床所見などを用い、原病の増悪の有無を判定する。ただし、画像診断は 2 コース毎で可とする。

5-3. 判定基準

画像上の PD(進行)、腫瘍マーカー効果判定による PD、臨床的増悪を増悪と判定する。

6. Endpoint と統計学的考察

1) Primary endpoint: 生存期間

2) Secondary endpoint: 完全腫瘍消失割合、無増悪生存期間、薬物有害反応、手術合併症割合、開腹手術回数、総開腹手術時間、周術期輸血量、周術期血漿製剤使用量

3) 予定登録数: 各群 150 例、両群計 300 例