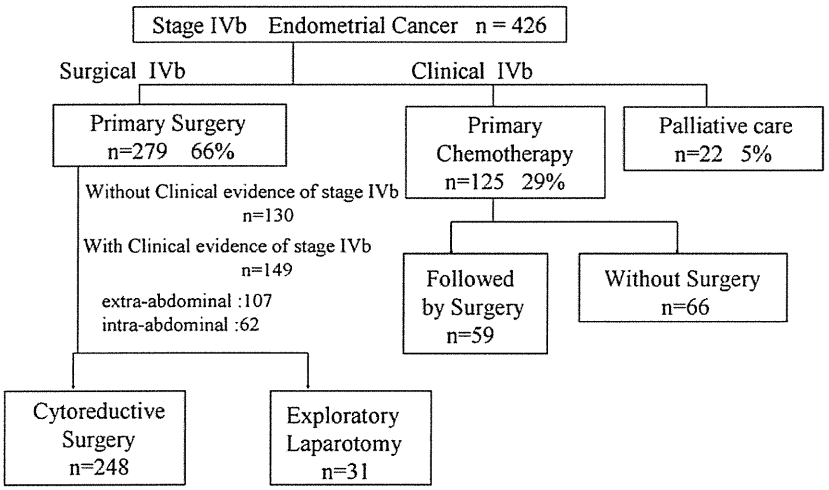

Fig. 1. Patients with stage IVb endometrial cancer, grouped according to initial treatment.

Table 1
Clinicopathological characteristics ($n = 426$).

Characteristics	Primary surgery		Primary chemotherapy		Palliative care		Total		Fisher's exact-test
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*p*-Value[c]
Median age, years (range)	59	(30–89)	58	(30–83)	73	(53–84)	59	(30–89)	
ECOG performance status									
0/1	253	(91)	97	(77)	7	(32)	357	(84)	0.002
2–4	25	(9)	26	(21)	15	(68)	66	(15)	
Unknown	1	(<1)	2	(2)	0	(0)	3	(1)	
Body mass index									
<20	51	(18)	32	(26)	9	(40)	92	(22)	0.311
20 ≤ 25	135	(48)	57	(45)	5	(23)	197	(46)	
≥25	80	(29)	34	(27)	6	(28)	120	(28)	
Unknown	13	(5)	2	(2)	2	(9)	17	(4)	
Diabetes mellitus									
Yes	23	(8)	23	(18)	4	(18)	50	(12)	0.003
No	251	(90)	95	(76)	17	(77)	364	(85)	
Unknown	5	(2)	7	(6)	1	(5)	13	(3)	
Hypertension									
Yes	54	(19)	35	(28)	10	(45)	99	(23)	0.049
No	219	(78)	84	(67)	11	(50)	314	(74)	
Unknown	6	(3)	6	(5)	1	(5)	13	(3)	
Histology									
Endometrioid	163	(58)	68	(54)	14	(64)	245	(58)	0.514
Non-endometrioid	116	(42)	57	(46)	8	(36)	181	(42)	
Extra-abdominal metastases									
Negative	172	(62)	22	(18)	3	(14)	197	(46)	<0.001
Positive	107	(38)	103	(82)	19	(86)	229	(54)	
Number of regions									
1	83	(29)	49	(39)	7	(32)	139	(33)	
≥2	24	(9)	54	(43)	12	(54)	90	(21)	
Clinical intra-abdominal stage IVb metastases									
Negative	217	(78)	60	(48)	11	(50)	288	(68)	<0.001
Positive	62	(22)	65	(52)	11	(50)	138	(32)	
Treatment									
Surgery	279	(100)	59	(47)	0	(0)	338	(79)	
Hysterectomy	248	(89)	53	(42)			301	(70)	
No hysterectomy	31	(11)	6	(5)			37	(9)	
Chemotherapy	238	(85)	125	(100)	0	(0)	363	(86)	
Taxanes + platinum	135	(48)	78	(63)			213	(50)	
AP ± α	84	(30)	38	(30)			122	(29)	
Others	19	(7)	9	(7)			28	(7)	
Radiotherapy	42	(15)	28	(22)	9	(41)	79	(19)	
ERT: Pelvis	28	(10)	19	(15)	8	(36)			
ERT: PAN	16	(6)	4	(3)	3	(14)			
ERT: Others[a]	12	(4)	18	(15)	3	(15)			
ICRT	3	(1)	3	(2)	2	(9)			
Chemotherapy + radiotherapy[b]	31	(11)	28	(22)	0	(0)	59	(14)	

AP ± α, doxorubicin + platinum ± others; ERT, external radiotherapy; ICRT, intracavitary irradiation.
[a] Others included ERT to whole abdomen, supraclavicular, bone and brain.
[b] These patients are also included in the chemotherapy group and the radiotherapy group.
[c] *p*-Value, primary surgery group vs. primary chemotherapy group.

Table 2
Univariate analyses for overall survival.

Variable	n	(%)[a]	Median OS (months)	
			(95% CI)	Log-rank p^b
Age				
≤59	220	(52)	22 (17–27)	
≥60	206	(48)	12 (11–14)	0.0013
ECOG performance status				
0–1	357	(84)	19 (15–23)	
2–4	66	(15)	4 (2–5)	<0.0001
Diabetes mellitus				
Yes	50	(12)	13 (11–15)	
No	363	(85)	5 (3–7)	0.3761
Hypertension				
Yes	99	(23)	17 (12–23)	
No	314	(74)	14 (9–19)	0.7702
Histology				
Endometrioid	245	(58)	24 (19–29)	
Non-endometrioid	181	(42)	9 (8–11)	<0.0001
Extra-abdominal metastasis				
Positive	229	(54)	11 (9–14)	
Negative	197	(46)	21 (16–26)	0.0494
Clinical intra-abdominal stage IVb metastasis				
Positive	138	(32)	9 (6–12)	
Negative	288	(68)	20 (15–26)	<0.0001
Initial treatment				
Primary surgery	279	(65)	21 (17–26)	
Primary chemotherapy	125	(29)	12 (9–15)	
Palliative care	22	(6)	1 (0–4)	<0.0001
Hysterectomy				
Yes	301	(71)	24 (20–28)	
No	125	(29)	5 (4–7)	<0.0001
Chemotherapy				
Yes	363	(85)	18 (14–22)	
No	63	(15)	5 (3–7)	<0.0001
Radiotherapy				
Yes	79	(19)	12 (6–17)	
No	347	(81)	15 (12–19)	0.8958

ECOG, Eastern Cooperative Oncology Group.
[a] Numbers may not add up to totals because some data are unknown.
[b] Patients with unknown status were excluded in the calculation of log-rank p values.

only 62 (28%) had clinical intra-abdominal stage IVb disease detected by preoperative imaging examinations.

Treatment modalities

In the primary surgery group, 249 patients (89%) underwent postoperative adjuvant therapy, including 207 who underwent chemotherapy alone, 11 who underwent radiotherapy alone, and 31 who underwent both chemotherapy and radiotherapy. In the primary chemotherapy group, 59 patients underwent subsequent surgery, of which 52 also received postoperative radiotherapy or chemotherapy. Of the 66 patients who did not undergo surgery after primary chemotherapy, 21 also received radiotherapy.

The most common chemotherapy regimen was taxanes + platinum ± doxorubicin, followed by doxorubicin + cisplatin ± cyclophosphamide/ifosfamide. The treatment details are shown in Table 1.

Treatment outcomes

The median follow-up time among the censored patients was 41 months, and the median OS for all stage IVb EMCA patients was 14 months (95% confidence interval [CI]: 11–18). The causes of death were EMCA in 301 patients, other disease in 4, and unknown in 6. At the last follow-up, 62 patients were alive with no evidence of disease, 45 were alive with disease, and 8 were alive with unknown disease status. There were no treatment-related deaths.

Univariate and multivariate analyses

Univariate analyses of the relationships between OS and the demographic, clinicopathological, and therapeutic variables found that age, PS, histology, extra-abdominal metastasis, clinical intra-abdominal stage IVb metastasis, initial treatment, hysterectomy, and chemotherapy were significantly associated with OS (Table 2).

The median OS was 21 months (95% CI: 17–26) in the primary surgery group, 12 months (95% CI: 9–15) in the primary chemotherapy group, and 1 month (95% CI: 0–4) in the palliative care group ($p < 0.0001$; Fig. 2A).

Cox multivariate analysis showed that PS, histology, clinical intra-abdominal stage IVb metastasis, hysterectomy, and chemotherapy were independent prognostic factors for OS (Table 3).

Subgroup analysis

To explore the impact of preoperative chemotherapy, we analyzed the clinicopathological characteristics of patients who underwent primary chemotherapy followed by surgery, and compared the OS in this group with the OS in the primary surgery group.

Patients who underwent primary chemotherapy followed by surgery had a better PS and a lower rate of two or more extra-abdominal

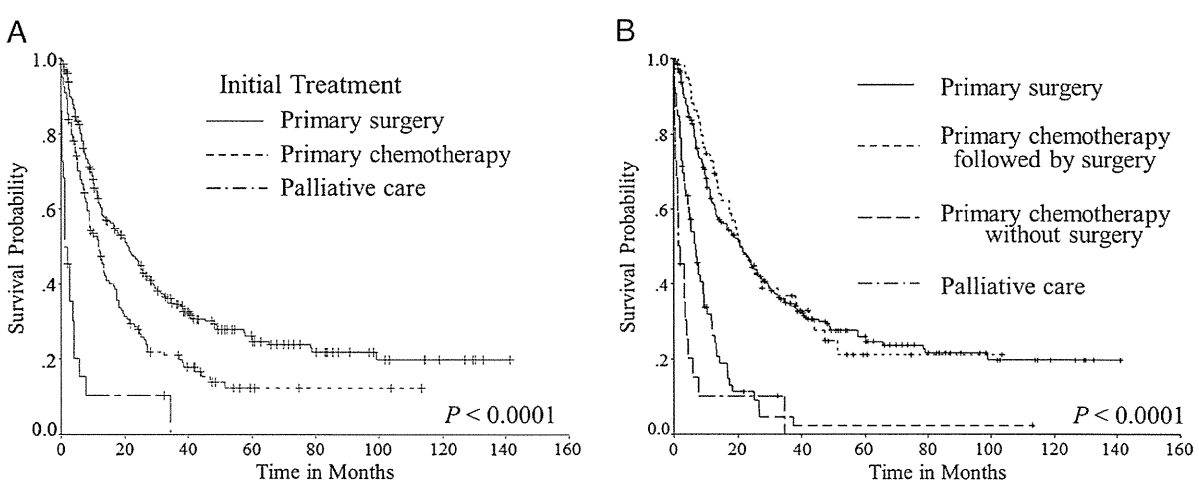

Fig. 2. Kaplan–Meier curves for overall survival (OS). A: Median OS according to initial treatment in patients with stage IVb endometrial cancer ($n = 426$): primary surgery group (solid line), 21 months; primary chemotherapy group (dotted line), 12 months; and palliative care group (dash-dot line), 1 month. B: Median OS of patient groups, showing the two primary chemotherapy subgroups: primary chemotherapy followed by surgery (dotted line), 21 months; and primary chemotherapy without surgery (dashed line), 7 months.

Table 3
Multivariate analyses.

Variable	Hazard ratio	95% CI	*p*-Value
ECOG performance status			
0–1 vs. 2–4	1.837	1.353–2.495	<0.001
Histology			
Endometrioid vs. non-EM	2.015	1.601–2.537	<0.001
Clinical intra-abdominal stage IVb metastasis			
Negative vs. positive	1.514	1.175–1.951	0.001
Hysterectomy			
No vs. yes	0.324	0.250–0.420	<0.001
Chemotherapy			
No vs. yes	0.449	0.327–0.618	<0.001

ECOG, Eastern Cooperative Oncology Group.

metastases than those who underwent primary chemotherapy without subsequent surgery ($p < 0.0001$) (Table S1), and had similar characteristics to those who underwent primary surgery, except for disease distribution. Of the 59 patients who underwent primary chemotherapy followed by surgery, 24 (40%) had non-endometrioid histology. Preoperatively, 57 patients (97%) received chemotherapy alone, and 2 patients received both chemotherapy and radiotherapy. Chemotherapy with taxane + platinum was administered to 58% of patients. The response to preoperative chemotherapy was as follows: complete or partial response in 40 patients, stable disease in 9 patients, progressive disease in 7 patients, and not evaluable in 3 patients. The median time from the start of chemotherapy to surgery was 99 days (range: 29–297 days). Postoperative therapy was as follows: chemotherapy alone in 44 patients, radiotherapy alone in 2 patients, both chemotherapy and radiotherapy in 5 patients, and no adjuvant treatment in 8 patients.

Table 4 shows the surgical procedures performed in the primary surgery group and in the group who underwent primary chemotherapy followed by surgery. Hysterectomy was performed in 89% ($n = 248$) of the primary surgery group and 90% ($n = 53$) of the group who underwent primary chemotherapy followed by surgery. In addition to hysterectomy and bilateral salpingo-oophorectomy, most patients underwent cytoreductive procedures with the intent of achieving maximum cytoreduction, including omentectomy, lymph node biopsy, resection of peritoneal dissemination, and colonic resection. The procedures performed were similar in both groups. Optimal cytoreduction (≤1 cm residual disease) was achieved in 45% ($n = 126$) of the primary surgery group and 57% ($n = 34$) of the group who underwent primary chemotherapy followed by surgery ($p = 0.087$).

Table 4
Surgical procedures and outcomes of surgery in the primary surgery group and the primary chemotherapy group.

	Primary surgery		Primary CT followed by surgery	
	($n = 279$)		($n = 59$)	
	n	(%)	*n*	(%)
Procedures performed				
Hysterectomy + BSO	248	(89)	53	(90)
Type of hysterectomy				
Simple	184	(66)	29	(49)
Subtotal	9	(3)	0	(0)
Modified-radical	49	(18)	24	(41)
Radical	6	(2)	0	(0)
Omentectomy/biopsy	180	(65)	35	(60)
Pelvic lymphadenectomy	158	(57)	31	(53)
Para-aortic lymphadenectomy	83	(30)	25	(42)
Resection of peritoneum	95	(34)	19	(32)
Appendectomy	30	(11)	5	(9)
Resection of colon/ileum	17	(6)	3	(5)
Colostomy/ileostomy	3	(2)	1	(2)
Diaphragm peritonectomy	1	(<1)	0	(0)
Resection of internal iliac artery	1	(<1)	0	(0)
Splenectomy	1	(<1)	1	(2)
Resection of liver	0	(0)	1	(2)
Mastectomy	1	(<1)	0	(0)
Resection of umbilicus/skin meta	4	(1)	0	(0)
Resection of supraclavicular LN	3	(1)	0	(0)
Resection of inguinal LN	7	(3)	0	(0)
Results of surgery				
Postoperative residual disease				
None	61	(22)	19	(32)
≤1 cm	65	(23)	15	(25)
>1 cm	153	(55)	25	(43)

BSO, bilateral salpingo-oophorectomy; CT, chemotherapy.

Three patients in the primary surgery group and one patient who underwent primary chemotherapy followed by surgery died within 30 days after surgery, all because of disease progression. Three of these four patients underwent exploratory laparotomy without further surgery, and the other patient had >2 cm residual disease. One life-threatening postoperative complication (pulmonary embolism) was reported in a patient who underwent primary chemotherapy followed by surgery.

The survival curves of the group who underwent primary chemotherapy followed by surgery and the primary surgery group were almost the same ($p = 0.8351$) (Fig. 2B).

Discussion

Few studies to date have included both surgically and non-surgically treated patients with stage IVb EMCA [16–19]. In our multicenter study of patients with stage IVb EMCA, we previously evaluated the role of treatment with cytoreductive surgery in 248 patients [12]. In the current study, we analyzed all 426 patients with stage IVb EMCA, including those who did not undergo surgery. This is the largest study of the overall population of patients with stage IVb EMCA.

The relationships between clinicopathological data and survival in the overall population of patients with stage IVb EMCA have not been well evaluated. The largest previously reported study was conducted by Aalders et al. [20] in 1984 and included 83 patients. In contrast to our study population, their patients were treated primarily by radiotherapy. They found that patients with well- and moderately differentiated adenocarcinoma had a better response rate than those with poorly differentiated adenocarcinoma [20]. Our previous analysis of 248 patients who underwent cytoreductive surgery examined the precise distribution of intra-abdominal disease and histopathological factors, and found that lower grade endometrioid type EMCA was an independent prognostic factor [12]. As the present study included patients who did not undergo surgery, we could not obtain detailed clinicopathological data such as the grade and precise distribution of disease in all cases, but we still found that endometrioid histology was an independent favorable prognostic factor in the overall population of those with stage IVb EMCA.

Our study identified some factors that should be considered during therapeutic decision making in stage IVb EMCA. First, clinical intra-abdominal stage IVb metastasis was a poor prognostic factor. Landrum et al. [21] conducted a case control study that compared intra-abdominal stage IVb EMCA with stage IIIc ovarian cancer, which has a similar metastatic pattern. They found that the 2-year OS was lower in EMCA than in ovarian cancer (52% vs. 76%, $p = 0.008$). However, as these two tumors may have different biological characteristics and chemosensitivities, the treatment strategies for stage IIIc ovarian cancer may not be equally suitable for intra-abdominal stage IVb EMCA.

Second, in our study of the overall population with stage IVb EMCA, 54% of patients had extra-abdominal metastasis. Most of the extra-abdominal metastases in EMCA were unresectable, in contrast to stage IV ovarian cancer where the most common site of stage-IV defining disease is pleural effusion [22]. The National Comprehensive Cancer Network Guidelines recommend palliative hysterectomy with or without

chemotherapy, radiotherapy, or hormonal therapy for extra-abdominal disease [23]. A systematic review of the Cochrane collaboration reported that combination chemotherapy improves survival in advanced EMCA [24]. Our previous analysis found that intra-abdominal optimal cytoreductive surgery and adjuvant therapy were prognostic factors even in the presence of extra-abdominal metastasis [12]. In the present study, chemotherapy and hysterectomy were identified as independent prognostic factors in patients with stage IVb EMCA. Our findings suggest that hysterectomy may be useful even in patients with unresectable extra-abdominal metastasis.

Similar to the direction of treatment for advanced ovarian cancer, several studies have reported that cytoreductive surgery was useful in advanced EMCA [3–10,25,26]. However, many patients do not undergo primary surgery for stage IVb EMCA, including 36% of the patients in the study by Numazaki et al. [27] and 34% of the patients in our study. In previous small series, 17–59% of patients with stage IV EMCA did not undergo surgery [16–19]. In these patients, surgery may not be selected as the initial treatment for various reasons including extra-abdominal metastasis, unresectable intra-abdominal disease, and medical comorbidities. Goff et al. [5] reported that surgical cytoreduction was not selected because of extra-abdominal metastasis in 8 of the 18 patients who did not undergo surgical cytoreduction. In our retrospective study, varying criteria were used for selecting chemotherapy as the initial treatment. It seems that chemotherapy was more likely to be chosen as the initial treatment than surgery in patients with poor PS, complications, and two or more extra-abdominal metastases.

In advanced ovarian cancer, NACT was first used as an alternative to primary debulking surgery in patients with apparently unresectable tumors or poor PS [28,29]. The indications for NACT were subsequently extended to include all cases of advanced disease, including patients with resectable tumors and good PS. The phase III NACT trial reported noninferior survival with less serious morbidity in the NACT arm [14].

Vandenput et al. [15] conducted the first prospective study of NACT in patients with serous EMCA with transperitoneal spread diagnosed by laparoscopy. Thirty patients received 3–4 cycles of NAC, of whom 24 underwent optimal cytoreduction. The median OS was 23 months. NACT therefore resulted in a high rate of optimal debulking surgery in these patients. In our study, only 59 patients (47%) in the primary chemotherapy group subsequently underwent surgery. The primary chemotherapy group included patients who were treated with the intent of progressing to NACT as well as patients who underwent chemotherapy with palliative intent only. Interestingly, the OS was comparable between the group who underwent primary chemotherapy followed by surgery and the primary surgery group. Of the patients who underwent chemotherapy or radiotherapy without surgery, only a few survived for a long time.

The study of NACT by Vandenput et al. [15] was limited to patients with intra-abdominal stage IVb EMCA, whereas in our study, 40 (68%) of the patients who underwent primary chemotherapy followed by surgery had extra-abdominal disease. Our findings suggest that NACT may be a useful treatment option for highly selected patients with intra-abdominal or extra-abdominal stage IVb EMCA. However, EMCA is less chemosensitive than ovarian cancer, and NACT is not necessarily suitable for all patients with advanced EMCA. Preoperative chemotherapy can show whether the tumor is chemosensitive, and the morbidity associated with surgery can then be avoided in patients with chemoresistant tumors. Preoperative chemotherapy can therefore be used to determine which patients are suitable candidates for NACT.

This study may have a selection bias and has several limitations. First, the quality of data may not be uniform because of the retrospective, multi-center design. We made a considerable effort to standardize data collection using a case report form. Second, interpretation of the results is difficult because decisions regarding initial treatment may vary among institutions. Third, it is unknown which patients in the primary chemotherapy group received initial chemotherapy with the intent of proceeding to NACT. Therefore, the group who underwent primary chemotherapy followed by surgery is not the same as a NACT group. Only a prospective trial can definitively determine the role of NACT in advanced EMCA.

In conclusion, our results show the current status of treatment for the overall population of patients with stage IVb EMCA in Japan. Good PS, endometrioid histology, absence of clinical intra-abdominal stage IVb disease, hysterectomy, and chemotherapy were identified as independent prognostic factors for survival. These findings suggest that combined hysterectomy and chemotherapy may benefit selected patients with stage IVb EMCA. Subgroup analysis found that OS was similar between patients who underwent primary chemotherapy followed by surgery and those who underwent primary surgery. Our data suggest that preoperative chemotherapy may be a useful treatment choice for patients with stage IVb EMCA who are not suitable for primary surgery.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2013.08.036.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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References

[1] Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet 2005;366(9484):491–505.
[2] Rose PG. Endometrial carcinoma. N Engl J Med 1996;335(9):640–9.

[3] Ayhan A, Taskiran C, Celik C, Yuce K, Kucukali T. The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer. Int J Gynecol Cancer 2002;12(5):448–53.
[4] Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol 2000;78(2):85–91.
[5] Goff BA, Goodman A, Muntz HG, Fuller Jr AF, Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol 1994;52(2):237–40.
[6] Chi DS, Welshinger M, Venkatraman ES, Barakat RR. The role of surgical cytoreduction in stage IV endometrial carcinoma. Gynecol Oncol 1997;67(1):56–60.
[7] Shih KK, Yun E, Gardner GJ, Barakat RR, Chi DS, Leitao Jr MM. Surgical cytoreduction in stage IV endometrioid endometrial carcinoma. Gynecol Oncol 2011;122(3):608–11.
[8] Bristow RE, Duska LR, Montz FJ. The role of cytoreductive surgery in the management of stage IV uterine papillary serous carcinoma. Gynecol Oncol 2001;81(1):92–9.
[9] Thomas MB, Mariani A, Cliby WA, Keeney GL, Podratz KC, Dowdy SC. Role of cytoreduction in stage III and IV uterine papillary serous carcinoma. Gynecol Oncol 2007;107(2):190–3.
[10] Ueda Y, Enomoto T, Miyatake T, Egawa-Tanaka T, Ugaki H, Yoshino K, et al. Endometrial carcinoma with extra-abdominal metastasis: improved prognosis following cytoreductive surgery. Ann Surg Oncol 2010;17(4):1111–7.
[11] Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. Gynecol Oncol 2010;118(1):14–8.
[12] Eto T, Saito T, Kasamatsu T, Nakanishi T, Yokota H, Satoh T, et al. Clinicopathological prognostic factors and the role of cytoreduction in surgical stage IVb endometrial cancer: a retrospective multi-institutional analysis of 248 patients in Japan. Gynecol Oncol 2012;127(2):338–44.
[13] Creasman W, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Cancer of the corpus uteri. FIGO 6th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 2006;95(Suppl. 1):S105–43.
[14] Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363(10):943–53.
[15] Vandenput I, Van Calster B, Capoen A, Leunen K, Berteloot P, Neven P, et al. Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): a new preferred treatment? Br J Cancer 2009;101(2):244–9.
[16] Cook AM, Lodge N, Blake P. Stage IV endometrial carcinoma: a 10 year review of patients. Br J Radiol 1999;72(857):485–8.
[17] Pliskow S, Penalver M, Averette HE. Stage III and stage IV endometrial carcinoma: a review of 41 cases. Gynecol Oncol 1990;38(2):210–5.
[18] Behbakht K, Yordan EL, Casey C, DeGeest K, Massad LS, Kirschner CV, et al. Prognostic indicators of survival in advanced endometrial cancer. Gynecol Oncol 1994;55(3):363–7.
[19] van Wijk FH, Huikeshoven FJ, Abdulkadir L, Ewing PC, Burger CW. Stage III and IV endometrial cancer: a 20-year review of patients. Int J Gynecol Cancer 2006;16(4):1648–55.
[20] Aalders JG, Abeler V, Kolstad P. Stage IV endometrial carcinoma: a clinical and histopathological study of 83 patients. Gynecol Oncol 1984;17(1):75–84.
[21] Landrum LM, Moore KN, Myers TK, Lanneau Jr GS, McMeekin DS, Walker JL, et al. Stage IVB endometrial cancer: does applying an ovarian cancer treatment paradigm result in similar outcomes? A case-control analysis. Gynecol Oncol 2009;112(2):337–41.
[22] Bonnefoi H, A'Hern RP, Fisher C, Macfarlane V, Barton D, Blake P, et al. Natural history of stage IV epithelial ovarian cancer. J Clin Oncol 1999;17(3):767–75.
[23] NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®). http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf; 2013. [cited Version 1.2013 18.3.2013]; Available from:.
[24] Humber CE, Tierney JF, Symonds RP, Collingwood M, Kirwan J, Williams C, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann Oncol 2007;18:409–20.
[25] Lambrou NC, Gomez-Marin O, Mirhashemi R, Beach H, Salom E, Almeida-Parra Z, et al. Optimal surgical cytoreduction in patients with stage III and stage IV endometrial carcinoma: a study of morbidity and survival. Gynecol Oncol 2004;93(3):653–8.
[26] Memarzadeh S, Holschneider CH, Bristow RE, Jones NL, Fu YS, Karlan BY, et al. FIGO stage III and IV uterine papillary serous carcinoma: impact of residual disease on survival. Int J Gynecol Cancer 2002;12(5):454–8.
[27] Numazaki R, Miyagi E, Konnai K, Ikeda M, Yamamoto A, Onose R, et al. Analysis of stage IVB endometrial carcinoma patients with distant metastasis: a review of prognoses in 55 patients. Int J Clin Oncol 2009;14(4):344–50.
[28] Chambers JT, Chambers SK, Voynick IM, Schwartz PE. Neoadjuvant chemotherapy in stage X ovarian carcinoma. Gynecol Oncol 1990;37(3):327–31.
[29] Jacob JH, Gershenson DM, Morris M, Copeland LJ, Burke TW, Wharton JT. Neoadjuvant chemotherapy and interval debulking for advanced epithelial ovarian cancer. Gynecol Oncol 1991;42(2):146–50.

FULL PAPER

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Keywords: S-1; long-term; adjuvant chemotherapy; non-small cell lung cancer

Feasibility trial for adjuvant chemotherapy with docetaxel plus cisplatin followed by single agent long-term administration of S-1 chemotherapy in patients with completely resected non-small cell lung cancer: Thoracic Oncology Research Group Study 0809

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Background: We conducted a multicentre feasibility study for single agent long-term S-1 chemotherapy following docetaxel plus cisplatin in patients with curatively resected stage II–IIIA non-small cell lung cancer.

Methods: Patients received three cycles of docetaxel (60 mg m^{-2}) plus cisplatin (80 mg m^{-2}) and then received S-1 (40 mg m^{-2} twice daily) for 14 consecutive days with a 1-week rest for >6 months (maximum, 1 year). The primary end point was feasibility, which was defined as the proportion of patients who completed eight or more cycles of S-1 chemotherapy. If the lower 95% confidence interval (CI) of this proportion was 50% or more, then the treatment was considered as feasible. The sample size was set at 125 patients.

Results: One hundred and thirty-one patients were enrolled, of whom 129 patients were eligible and assessable. In all, 109 patients (84.5%) completed 3 cycles of docetaxel plus cisplatin and 66 patients (51.2%, 95% CI: 42.5–59.8) completed 8 or more cycles of S-1 treatment. Grade 3/4 toxicities during the S-1 chemotherapy included anaemia (7.3%), neutropaenia (3.7%), and anorexia (3.7%).

Conclusion: The toxicity level was acceptable, although the results did not meet our criterion for feasibility. Modification of the treatment schedule for S-1 chemotherapy might improve the treatment compliance.

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Primary surgery is the standard of care for resectable clinical stage I or II non-small cell lung cancer (NSCLC). The 5-year survival rate for patients with clinical stage IB and stage II surgically resected NSCLC was ~66% and 50%, respectively. The majority of patients with recurrences have distant metastases, indicating that systemic micrometastases are common in patients with completely resected NSCLC. To control distant micrometastasis and to improve patients' survival, adjuvant chemotherapy has been examined in patients with completely resected NSCLC of pathological stage I–III. Several randomised studies and meta-analyses have demonstrated that cisplatin-based adjuvant chemotherapy improved the overall survival (OS) in patients with pathological stage IB to III NSCLC (Arriagada *et al*, 2004; Hotta *et al*, 2004; Winton *et al*, 2005; Douillard *et al*, 2006; Pignon *et al*, 2006). However, the absolute increase in survival was only 4% at 5 years. Thus, new treatment strategies or drugs are needed to improve the clinical outcome in patients with resectable NSCLC.

A randomised phase III study demonstrated that adjuvant chemotherapy with uracil-tegafur (UFT) improved survival among patients with completely resected pathological stage I adenocarcinoma of the lung. The 5-year OS was 88% in the UFT group and 85% in the control group (hazard ratio 0.71, 95% confidence interval (CI) 0.52–0.98) (Kato *et al*, 2004). S-1 is an oral anticancer agent comprises tegafur, gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxicity of fluorouracil) in a molar ratio of 1 : 0.4 : 1 (Shirasaka *et al*, 1996). S-1 is approved for the treatment of NSCLC as well as gastric, colorectal, head and neck, breast, pancreatic, and biliary tract cancer in Japan. In a phase II trial, S-1 monotherapy produced a response rate of 22% as a first-line treatment in patients with advanced NSCLC (Kawahara *et al*, 2001). S-1 is believed to have a stronger antitumour activity against NSCLC than UFT, since UFT monotherapy produced a response rate of only 6% in another phase II study (Keicho *et al*, 1986). A randomised phase III trial demonstrated that S-1 plus carboplatin (CBDCA) was non-inferior in terms of OS, compared with paclitaxel plus CBDCA, in patients with advanced NSCLC (Okamoto *et al*, 2010). Another randomised phase III trial also demonstrated that S-1 plus CDDP was non-inferior in terms of OS, compared with docetaxel plus CDDP, in patients with advanced NSCLC (Katakami *et al*, 2012). Previous phase II trials demonstrated that S-1 monotherapy produced a response rate of 7–14% as a second-line treatment for advanced NSCLC (Totani *et al*, 2009; Govindan *et al*, 2011; Shiroyama *et al*, 2011).

Recent phase III trials have demonstrated that switch maintenance chemotherapy consisting of pemetrexed or erlotinib prolonged the OS of patients with advanced NSCLC who showed no signs of progression after four cycles of platinum-based chemotherapy (Ciuleanu *et al*, 2009; Cappuzzo *et al*, 2010). Continuation maintenance with pemetrexed also prolonged the OS in patients with non-squamous NSCLC in another randomised trial (Paz-Ares *et al*, 2012a,b). Maintenance chemotherapy has thus received considerable attention.

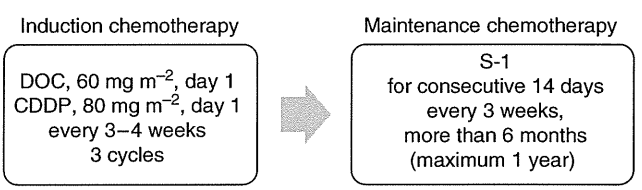
The Thoracic Oncology Research Group (TORG) conducted a randomised phase II study comparing docetaxel (DOC) plus CDDP with paclitaxel (PTX) plus CBDCA as an adjuvant chemotherapy in patients with completely resected stage IB to IIIA NSCLC (TORG 0503). This study showed that DOC plus CDDP had a promising activity with a favourable 2-year recurrence-free survival (RFS) rate (74.1% *vs* 72.5%, respectively) (Ohira *et al*, 2011). Taking these rationales into consideration, we conducted a feasibility study for adjuvant chemotherapy consisting of DOC plus CDDP followed by single agent long-term S-1 chemotherapy in patients with completely resected NSCLC (TORG 0809).

PATIENTS AND METHODS

Patient population. Patients were required to have completely resected stage II or IIIA (according to the Union Internationale Contre le Cancer (UICC) fifth TNM edition) NSCLC, an age of 20–74 years, and an ECOG performance status (PS) of 0 or 1. Other criteria included a PaO_2 at room air $\geqslant$70 torr or an SpO_2 at room air $\geqslant$95%, and adequate organ function (i.e., total bilirubin $\leqslant$1.2 mg dl^{-1}, AST and ALT $\leqslant$100 IU l^{-1}, serum creatinine $\leqslant$1.2 mg dl^{-1}, creatinine clearance $\geqslant$60 ml min^{-1}, leukocyte count $\geqslant$4000 per mm^3 and $\leqslant$12 000 per mm^3, neutrophil count $\geqslant$2000 per mm^3, haemoglobin $\geqslant$10.0 g dl^{-1}, and platelets $\geqslant$100 000 per mm^3). Patients were required to start the protocol treatment within 10 weeks after surgical resection.

Key exclusion criteria were a lack of recovery from surgical complications; active infection; interstitial pneumonia as determined using computed tomography (CT) of the chest; acute cardiac infarction within 6 months; uncontrolled heart disease, liver dysfunction, or diabetes mellitus; grade 2 or worse peripheral neuropathy; active concomitant malignancy; pregnancy or breast-feeding; a history of hypersensitivity to drugs including polysorbate-80; and the concurrent use of flucytosine. Patients who had undergone a pneumonectomy were also excluded. All the patients were required to provide written informed consent.

Treatment plan. The treatment schema is shown in Figure 1. Treatment was started within 1 week after enrolment in the study. Patients received adjuvant chemotherapy with DOC (60 mg m^{-2}, day 1) and CDDP (80 mg m^{-2}, day 1) every 3–4 weeks for up to three cycles. After the completion of adjuvant chemotherapy with DOC plus CDDP, if the leukocyte count was $\geqslant$3000 per mm^3, the neutrophil count was $\geqslant$1500 per mm^3, the platelet count was $\geqslant$100 000 per mm^3, the AST and/or ALT level was $\leqslant$100 IU l^{-1}, the total bilirubin level was $\leqslant$1.5 mg dl^{-1}, the serum creatinine level was $<$1.5 mg dl^{-1}, and all other non-haematological toxicities were grade 1 or better with the exception of alopecia, body weight loss, and hyponatraemia, then the patients were treated with oral S-1 at a dose of 40 mg m^{-2} twice daily for 14 consecutive days, followed by a 1-week rest. The actual dose of S-1 was selected as follows: patients with a body surface area (BSA) of $<$1.25 m^2 received 80 mg daily; those with a BSA of 1.25 m^2 or more but $<$1.5 m^2 received 100 mg daily; and those with a BSA of 1.5 m^2 or more received 120 mg daily. If the serum creatinine level was 1.2 mg dl^{-1} or more but $<$1.5 mg dl^{-1} before the initiation of S-1 chemotherapy, then the S-1 dose was reduced to a lower level. This 3-week cycle was repeated for 6 months (maximum, 1 year) if neither unacceptable toxicity nor tumour recurrence was observed. In the event of a leukocyte count of $<$2000 per mm^3, a platelet count of $<$75 000 per mm^3, an AST and/or ALT level of $\geqslant$100 IU l^{-1}, a total bilirubin level of $\geqslant$2.5 mg dl^{-1}, a serum



	S-1
BSA $<$ 1.25 m^2	40 mg, b.i.d.
1.25 m^2 $\leqslant$ BSA $<$ 1.5 m^2	50 mg, b.i.d.
1.5 m^2 $\leqslant$ BSA	60 mg, b.i.d.

BSA, body surface area.

Figure 1. **Treatment schema for this study.**

creatinine level of $\geqslant 1.5\,mg\,dl^{-1}$, appetite loss, diarrhoea, mucositis, nausea/vomiting of grade 2 or worse despite appropriate antiemetic therapy, and/or other grade 2 non-haematological toxicities other than body weight loss, alopecia, or hyponatraemia, the daily dose of S-1 was reduced from 120 to 100 mg, 100 to 80 mg, or 80 to 50 mg in the next cycle. If the patients experienced the above-mentioned toxicities after the dose reduction, then their daily dose of S-1 was reduced from 100 to 80 mg, or 80 to 50 mg. If a patient with a BSA of $<1.25\,m^2$ experienced the above toxicities at 50 mg, then the S-1 chemotherapy was terminated. If the adjuvant chemotherapy of DOC + CDDP was terminated after one or two cycles, then a shift to S-1 chemotherapy was allowed. However, these patients were not considered to have completed the protocol treatment.

Safety assessment and follow-up. For the toxicity assessment, blood samples were obtained before the start of each cycle. A chest X-ray examination was performed monthly throughout the study period. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. A CT examination of the chest was performed at 1, 2, 3, and 5 years after the initiation of the protocol treatment.

Study design and statistical analysis. This trial was designed as a multicentre, prospective, single-arm, feasibility study and the study protocol was approved by the institutional review board of each participating institution. All the study data were managed by the TORG0809 data centre at Kitasato University Research Center for Clinical Pharmacology.

The primary end point of this study was feasibility, which was defined as the proportion of patients who had completed eight or more cycles of S-1 chemotherapy. If the lower 95% CI of this proportion was 50% or more, then the treatment was considered as feasible. If a patient received 75% or more of S-1 in a cycle, that is, 21 times per cycle, this patient was considered to have completed the treatment cycle. If 72 out of 120 patients (60%) completed the protocol treatment, then the 95% CI of the proportion of the treatment completion was 51.2–68.8%. Considering the possibility of ineligible patients, the sample size was set at 125 patients.

The secondary end points included adverse events, OS, RFS, and recurrence pattern. Because of the short follow-up period, we will report the OS and RFS data elsewhere. We plan to analyse the OS and RFS at 5 years after the last enrolment, as described in the study protocol. The statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

This study was registered with the UMIN Clinical Trials Registry (number UMIN000001779).

RESULTS

Patient population. A total of 131 patients were enrolled in this study between January 2009 and November 2010 from 20 institutions in Japan. One patient did not receive any protocol treatment at the patient's request. Another patient was enrolled as p-stage IIIA according to the UICC 7th edition; however, the p-stage corresponded to IIIB according to the UICC 5th edition, making this patient ineligible. This patient received three cycles of docetaxel plus cisplatin and two cycles of S-1 chemotherapy, and she was included in the safety analysis. A total of 129 patients were eligible (Figure 2). The patient characteristics are listed in Table 1. Sixty-four percent of the patients were male; the median age was 63 years. Seventy-eight percent of the patients had an adenocarcinoma histology.

Treatment delivery and protocol compliance. Overall, 114 patients received two cycles or more of DOC + CDDP. Of these, 67 patients (58.8%) required a dose reduction of DOC or CDDP. The most common reason for the dose reduction of DOC and CDDP was grade 4 neutropaenia ($n = 63$), followed by a fever of 38.0 °C or higher ($n = 16$). The dose of CDDP was reduced because of anorexia, nausea, and/or vomiting of grade 2 or worse for more than a week ($n = 16$) and an elevated serum creatinine level of $1.5\,mg\,dl^{-1}$ or more ($n = 6$).

In total, 109 patients (84.5%) completed three cycles of adjuvant chemotherapy consisting of DOC + CDDP (Table 2). The main reasons for the discontinuation of the adjuvant chemotherapy were toxicity ($n = 15$) and patient refusal because of toxicity ($n = 7$) (Table 3). One patient terminated the DOC + CDDP treatment after one cycle and completed eight cycles of S-1 chemotherapy. Another patient terminated the DOC + CDDP treatment after two cycles and received three cycles of S-1 chemotherapy.

One hundred and eight patients received S-1 chemotherapy. Of these, 34 patients (31.5%) required the interruption of S-1 during a treatment cycle. Thirty-one patients (28.7%) required a dose reduction of S-1. The majority of the reasons for the interruption

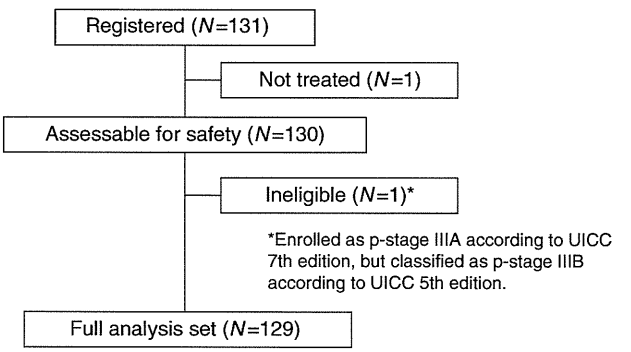


Figure 2. **CONSORT diagram.**

Table 1. Patient characteristics of 129 eligible patients

Characteristic	Number of patients
Sex	
Male	83
Female	46
Age (years)	
Median	63
Range	23–74
PS status	
0	107
1	22
Pathological stage[a]	
IIA	17
IIB	32
IIIA	80
Histological type	
Adenocarcinoma	100
Squamous cell carcinoma	25
Others	4

Abbreviations: PS = performance status; TNM = tumour-node-metastasis.
[a]Pathological stage was based on the Union Internationale Contre le Cancer fifth TNM edition.

or dose reduction of S-1 were appetite loss, diarrhoea, mucositis, or nausea/vomiting of grade 2 or worse ($n=27$), followed by other non-haematologic toxicities of grade 2 or worse ($n=20$).

One hundred and six patients (82.2%) completed three cycles of DOC + CDDP and subsequently switched to S-1 chemotherapy. Of these, 31 patients terminated the S-1 chemotherapy after receiving 3 or fewer cycles. A total of 66 patients (51.2%; 95% CI, 42.5–59.8%) completed 8 cycles or more of S-1 treatment (Table 2). The lower limit of the 95% CI for the completion rate was 42.5%, which was less than our previously defined criterion for treatment feasibility. The reasons for the discontinuation of the S-1 chemotherapy included toxicity ($n=17$), patient refusal because of toxicity ($n=15$), and recurrence ($n=6$) (Table 3).

Safety and toxicity. The most common grade 3 or 4 toxicity experienced during the DOC + CDDP treatment was neutropaenia (78.5%) (Table 4). Ten patients (7.7%) developed febrile neutropaenia; however, all these patients recovered after receiving appropriate antibiotic therapy. Two patients experienced grade 3 or 4 allergic reactions to DOC during the first cycle, resulting in treatment termination.

Grade 3 or 4 toxicities during the S-1 chemotherapy included anaemia (7.3%), neutropaenia (3.7%), anorexia (3.7%), dyspnoea (1.8%), and infection with neutropaenia of grade 0–2 (1.8%). Febrile neutropaenia was not observed. One treatment-related death occurred during the study. This patient was a 63-year-old man. After two cycles of S-1 chemotherapy, he developed grade 3 fatigue. On day 36 of the second cycle of S-1, grade 3 dyspnoea was observed, and his SpO_2 was 92% in room air. A CT scan of the chest revealed bilateral diffuse ground-glass opacities. Prednisolone (80 mg day^{-1}; 1 mg kg^{-1} per day) was administered, and an improvement in the opacities was observed. The prednisolone was tapered to 30 mg day^{-1} for 6 weeks; however, multiple cavity lesions were visible on a chest CT image obtained 2 months after the initiation of the steroid therapy. Multiple abscesses at the neck, axilla, chest, and femur were noted, and the patient developed hypotension. *Nocardia* was isolated in blood and abscess samples, with a diagnosis of disseminated nocardiosis. Sulfamethoxazole/trimethoprim and antibiotics were administered and artificial ventilation therapy was performed. The patient was taken off the respirator once, but the pneumonitis recurred and disseminated intravascular coagulation also developed, leading to death.

Table 2. Treatment delivery in 129 eligible patients

Treatment	Cycle	Number of patients	%	95% Confidence interval
Docetaxel + cisplatin	1	129	100	
	2	114	88.4	
	3	109	84.5	
Maintenance chemotherapy using S-1	1	106	82.2	
	2	97	75.2	
	3	86	66.7	
	4	75	58.1	
	5	73	56.6	
	6	72	55.8	
	7	71	55	
	8	67	51.9	
Completion		66	51.2	42.5–59.8

Table 3. Reason for discontinuation of the treatment

Reasons	Docetaxel + cisplatin	Maintenance chemotherapy using S-1
Recurrence	1	6
Toxicity	15	17
Patient refusal because of toxicity	7	15
Others	0	2

DISCUSSION

This feasibility study was designed to evaluate the tolerability, safety, and efficacy of single agent long-term administration of S-1 chemotherapy following three cycles of DOC plus CDDP in patients with completely resected stage II or IIIA NSCLC. Fifty-one percent of the patients (95% CI, 42.5–59.8%) completed three cycles of DOC plus CDDP and eight cycles or more of S-1 chemotherapy. The lower limit of the CI for this proportion was lower than the predefined criterion of 50%. Grade 3–4 haematologic toxicities were observed in 7.3% of patients, while grade 3–4 non-haematologic toxicities were observed in only 4%. However, grade 1–2 anorexia and/or fatigue were common, with rates of ~50–60%. S-1 was administered for 2 weeks with a 1-week rest. The long duration of S-1 administration might have been responsible for the low-grade but extended non-haematologic toxicities and might have been too intensive for patients especially after platinum-doublet chemotherapy. In a previous phase III study of adjuvant chemotherapy for gastric cancer with single agent of S-1, 78% of patients received S-1 for at least 6 months (Sakuramoto *et al*, 2007). Adjuvant chemotherapy of DOC + CDDP probably affected the compliance of S-1 chemotherapy negatively in our study. A modification of the treatment schedule for S-1 chemotherapy, such as a 2-week rest period rather than a 1-week rest period, might improve treatment compliance.

Efficacious treatment for advanced stage disease has been introduced and investigated in an adjuvant setting, such as bevacizumab plus platinum-doublet chemotherapy in patients with non-squamous cell carcinoma or erlotinib in patients with a mutated epidermal growth factor receptor gene. Recent phase III trials have demonstrated that switch maintenance chemotherapy consisting of pemetrexed or erlotinib, which were efficacious for second-line chemotherapy, prolonged the OS in patients with advanced NSCLC (Ciuleanu *et al*, 2009; Cappuzzo *et al*, 2010). Switch maintenance chemotherapy can be recognised as an early second-line chemotherapy. The purpose of adjuvant chemotherapy is to control micrometastasis and to prevent recurrence. Switch maintenance chemotherapy is considered to enhance the efficacy of adjuvant chemotherapy. Previous phase II trials have demonstrated that S-1 monotherapy produced a response rate of 7–14%, a median progression-free survival (PFS) of 3–4 months, and a median OS of 7–16 months as a second-line treatment for advanced NSCLC (Totani *et al*, 2009; Govindan *et al*, 2011; Shiroyama *et al*, 2011). Pemetrexed is effective against non-squamous NSCLC; on the other hand, S-1 is effective against both non-squamous and squamous NSCLC. A randomised trial comparing S-1 and docetaxel as a second- or third-line chemotherapy is now underway in Asia. Switch maintenance chemotherapy using S-1 is also being evaluated as a first-line chemotherapy for patients with advanced NSCLC in a phase II study (UMIN000003676). If promising RFS or OS data in this trial are obtained, then a prospective randomised trial will be warranted to compare adjuvant chemotherapy with or without single agent long-term administration of S-1 chemotherapy.

Table 4. Toxicity

	Docetaxel + cisplatin ($n = 130$)					Maintenance chemotherapy using S-1 ($n = 109$)					
Toxicity	**Toxicity grade**					**Toxicity grade**					
	1	2	3	4	%3–4	1	2	3	4	5	%3–5
Haematologic											
Neutropaenia	4	14	39	63	78.5	20	18	4	0	0	3.7
Anaemia	52	31	1	0	0.8	26	38	6	2	0	7.3
Thrombocytopaenia	30	6	0	0	0	35	0	0	0	0	0
Gastrointestinal											
Anorexia	55	47	22	0	16.9	43	21	4	0	0	3.7
Vomiting	23	20	5	0	3.8	11	5	1	0	0	0.9
Diarrhoea	35	11	15	0	11.5	19	3	1	0	0	0.9
Mucositis	12	4	0	0	0	23	7	0	0	0	0
Hepatic											
AST	14	5	2	0	1.5	25	5	0	0	0	0
ALT	25	9	1	0	0.8	24	4	0	0	0	0
Renal											
Creatinine	39	9	0	0	0	30	8	0	0	0	0
Neurologic											
Neuropathy (sensory)	9	4	0	0	0	19	2	2	0	0	1.8
Others											
Hyponatraemia	57	—	18	5	17.7	16	—	0	0	0	0
Fatigue	57	21	5	0	3.8	41	9	2	0	0	1.8
Allergic reaction	7	0	1	1	1.5	1	0	0	0	0	0
Dehydration	0	0	2	0	1.5	0	0	0	0	0	0
Alopecia	68	29	0	0	0	35	10	0	0	0	0
Febrile neutropaenia	—	—	10	0	7.7	—	—	0	0	0	0
Infection with G3–4 neutropaenia	0	3	5	0	3.8	0	0	0	0	0	0
Infection with G0–2 neutropaenia	0	3	2	1	2.3	1	3	1	0	1	1.8
Pneumonitis	1	0	0	0	0	0	1	1	0	0	0.9
Dyspnoea	0	1	0	0	0	8	2	2	0	0	1.8

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; G = grade.

A recent phase III trial has also demonstrated that continuation maintenance chemotherapy consisting of pemetrexed prolonged the OS and PFS in patients with advanced non-squamous NSCLC. However, concurrent chemoradiotherapy consisting of pemetrexed plus CDDP followed by four cycles of pemetrexed did not improve OS over concurrent chemoradiotherapy consisting of etoposide plus CDDP in patients with stage III non-squamous NSCLC (PROCLAIM study). Up to four cycles of pemetrexed in the PROCLAIM study, comparable to S-1 chemotherapy in our study, might be unable to enhance curative treatment effect. We might have to distinguish strategy for stage IV disease from that for curative situations in completely resected stage II/III disease.

Combination chemotherapy consisting of DOC plus CDDP is a standard regimen for the treatment of patients with advanced NSCLC. A randomised trial demonstrated that DOC + CDDP resulted in a more favourable response rate and OS than vinorelbine (VNR) plus CDDP in chemo-naïve patients with advanced NSCLC. The median OS period was 11.3 months for patients treated with DOC plus CDDP and 10.1 months for patients treated with VNR plus CDDP. The hazard ratio was 1.183 (97.2% CI, 0.989–1.416) (Fossella *et al*, 2003). A higher incidence of grade 3–4 anaemia, nausea, and vomiting was observed in VNR + CDDP arm, compared with DOC + CDDP arm. Febrile neutropaenia occurred in <5% of patients in both regimens. Furthermore, the single agent DOC had a more favourable OS period than the single agent VNR in both first-line and second-line settings in patients with advanced NSCLC (Fossella *et al*, 2000). TORG0503 study demonstrated that >90% of patients completed three planned cycles of adjuvant chemotherapy in both DOC + CDDP and PTX + CBDCA arms. On the other hand, the most common regimen for adjuvant chemotherapy for pathological stage II or III NSCLC is VNR + CDDP, because most randomised trials, which resulted in positive results, adopted VNR + CDDP. Considering the promising results of clinical trials for advanced NSCLC, it might be reasonable to select DOC + CDDP as an adjuvant chemotherapy in patients with completely resected stage II or III NSCLC. Indeed, DOC + CDDP has been selected as one of the standard adjuvant chemotherapy regimens in ECOG1505 study, which is a randomised phase III trial of adjuvant chemotherapy with or without bevacizumab in patients with completed resected early-stage NSCLC (Wakelee *et al*, 2011). However, 7.7% of patients experienced grade 3 febrile neutropaenia

during the chemotherapy of DOC + CDDP in our study. Relatively high incidence of febrile neutropaenia could not support the use of adjuvant chemotherapy with DOC + CDDP as a new alternative. Four cycles of VNR + CDDP followed by long-term administration of S-1 might be a better strategy in a future study.

The treatment cycle for DOC plus CDDP was set at three because the actual median numbers of cycles delivered in previous phase III studies of adjuvant chemotherapy were three or four (Winton *et al*, 2005; Douillard *et al*, 2006), and a randomised study demonstrated that four cycles or more of platinum-based chemotherapy did not improve the OS in patients with advanced NSCLC (Smith *et al*, 2001). In the TORG0503 study, the number of treatment cycles for DOC plus CDDP or for PTX plus CBDCA as an adjuvant chemotherapy was also set at three, and a favourable 2-year RFS rate was observed (Ohira *et al*, 2011).

A previous randomised phase II study demonstrated that adjuvant chemotherapy with pemetrexed plus CDDP was safe and feasible with less toxicity and superior dose delivery compared with VNR + CDDP (Kreuter *et al*, 2013). Pemetrexed plus CDDP is considered as suitable for adjuvant chemotherapy because of relatively less toxic and promising antitumour activity in patients with non-squamous NSCLC. A randomised phase III study is underway comparing pemetrexed plus CDDP and VNR + CDDP in patients with completely resected stage II–IIIA non-squamous NSCLC in Japan. However, it is difficult to conduct a randomised phase III study of adjuvant chemotherapy in patients with NSCLC, because large sample size and long-term follow-up are needed. Therefore, a randomised phase II study containing control arm should be taken into consideration to select appropriate experimental treatment.

Aprepitant, a standard antiemetic drug for cisplatin therapy, was approved in December 2009 in Japan. As a result, ~20 patients did not receive aprepitant. If aprepitant had been available for all the enrolled patients, then the treatment compliance might have improved. Furthermore, 2 out of the 129 patients experienced grade 3 or 4 allergic reactions to DOC during the first cycle, resulting in treatment termination. Premedication for DOC + CDDP included dexamethasone only on day 1 in this study. The administration of dexamethasone on the day before the initiation of DOC + CDDP and an antihistamine on day 1 might be recommended in future clinical trials to prevent anaphylaxis in response to DOC.

In conclusion, the toxicity level of S-1 chemotherapy was acceptable, although the treatment completion rate did not meet our criterion for feasibility. A modification of the treatment schedule for S-1 chemotherapy, such as a 2-week rest period rather than a 1-week rest period, might improve treatment compliance. After referring to the results for OS and RFS, we would like to plan a randomised trial to investigate whether platinum-based chemotherapy followed by single agent long-term administration of S-1 chemotherapy improves survival in patients with completely resected stage II or III NSCLC.

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REFERENCES

Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J (2004) Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* **350**(4): 351–360.

Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, Esteban E, Molinier O, Brugger W, Melezinek I, Klingelschmitt G, Klughammer B, Giaccone G (2010) Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* **11**(6): 521–529.

Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, Wu YL, Bover I, Begbie S, Tzekova V, Cucevic B, Pereira JR, Yang SH, Madhavan J, Sugarman KP, Peterson P, John WJ, Krejcy K, Belani CP (2009) Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* **374**(9699): 1432–1440.

Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzales-Larriba JL, Grodzki T, Pereira JR, Le Groumellec A, Lorusso V, Clary C, Torres AJ, Dahabreh J, Souquet PJ, Astudillo J, Fournel P, Artal-Cortes A, Jassem J, Koubkova L, His P, Riggi M, Hurteloup P (2006) Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 7(9): 719–727.

Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Belani CP (2003) Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* **21**(16): 3016–3024.

Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F, Hammershaimb L (2000) Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* **18**(12): 2354–2362.

Govindan R, Morgensztern D, Kommor MD, Herbst RS, Schaefer P, Gandhi J, Saito K, Zergebel C, Schiller J (2011) Phase II trial of S-1 as second-line therapy in patients with advanced non-small cell lung cancer. *J Thorac Oncol* **6**(4): 790–795.

Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M (2004) Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials. *J Clin Oncol* **22**(19): 3860–3867.

Katakami N, Gemma A, Sakai H, Kubota K, Nishio M, Inoue A, Okamoto H, Isobe H, Kunitoh H, Takiguchi Y, Kobayashi K, Nakamura Y, Ohmatsu H, Sugawara S, Minato K, Fukuda M, Yokoyama A, Takeuchi M, Michimae H, Kudoh S (2012) Randomized phase III trial of S-1 plus cisplatin versus docetaxel plus cisplatin for advanced non-small-cell lung cancer (TCOG0701). *J Clin Oncol* **30**(suppl): abstr 7515.

Kato H, Ichinose Y, Ohta M, Hata E, Tsubota N, Tada H, Watanabe Y, Wada H, Tsuboi M, Hamajima N, Ohta M (2004) A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* **350**(17): 1713–1721.

Kawahara M, Furuse K, Segawa Y, Yoshimori K, Matsui K, Kudoh S, Hasegawa K, Niitani H (2001) Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br J Cancer* **85**(7): 939–943.

Keicho N, Saijo N, Shinkai T, Eguchi K, Sasaki Y, Tamura T, Sakurai M, Sano T, Hoshi A (1986) Phase II study of UFT in patients with advanced non-small cell lung cancer. *Jpn J Clin Oncol* **16**(2): 143–146.

Kreuter M, Vansteenkiste J, Fischer JR, Eberhardt W, Zabeck H, Kollmeier J, Serke M, Frickhofen N, Reck M, Engel-Riedel W, Neumann S, Thomeer M, Schumann C, De Leyn P, Graeter T, Stamatis G, Zuna I, Griesinger F, Thomas M (2013) Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and

pemetrexed versus cisplatin and vinorelbine: the TREAT study. *Ann Oncol* **24**(4): 986–992.

Ohira T, Kubota K, Seto T, Kunitoh H, Shimada N, Ikeda N, Tsuboi M, Okamoto H, Masuda N, Maruyama R, Shibuya M (2011) A randomized phase II trial of adjuvant chemotherapy with docetaxel plus cisplatin versus paclitaxel plus carboplatin in patients with completely resected non-small cell lung cancer: TORG 0503. *J Thorac Oncol* **6**(suppl): S1555–S1556.

Okamoto I, Yoshioka H, Morita S, Ando M, Takeda K, Seto T, Yamamoto N, Saka H, Asami K, Hirashima T, Kudoh S, Satouchi M, Ikeda N, Iwamoto Y, Sawa T, Miyazaki M, Tamura K, Kurata T, Fukuoka M, Nakagawa K (2010) Phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer: results of a west Japan oncology group study. *J Clin Oncol* **28**(36): 5240–5246.

Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, Molinier O, Sahoo TP, Laack E, Reck M, Corral J, Melemed S, John W, Chouaki N, Zimmermann AH, Visseren-Grul C, Gridelli C (2012a) Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* **13**(3): 247–255.

Paz-Ares L, De Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, Molinier O, Sahoo TP, Laack E, Reck M, Jaime JC, Melemed S, John W, Chouaki N, Zimmermann AH, Visseren-Grul C, Gridelli C (2012b) PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed plus best supportive care versus placebo plus best supportive care immediately following induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small cell lung cancer. *J Clin Oncol* **30**(suppl): abstr LBA7507.

Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd F, Le Chevalier T (2006) Lung adjuvant cisplatin evaluation (LACE): A pooled analysis of five randomized clinical trials including 4,584 patients. *J Clin Oncol* **24**(18S Part I): 366s.

Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* **357**(18): 1810–1820.

Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, Fukushima M (1996) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* **7**(5): 548–557.

Shiroyama T, Komuta K, Imamura F, Hirashima T, Kijima T, Tachibana I, Kawase I (2011) Phase II study of S-1 monotherapy in platinum-refractory, advanced non-small cell lung cancer. *Lung Cancer* **74**(1): 85–88.

Smith IE, O'Brien ME, Talbot DC, Nicolson MC, Mansi JL, Hickish TF, Norton A, Ashley S (2001) Duration of chemotherapy in advanced non-small-cell lung cancer: a randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. *J Clin Oncol* **19**(5): 1336–1343.

Totani Y, Saito Y, Hayashi M, Tada T, Kohashi Y, Mieno Y, Kato A, Imizu H, Yoneda Y, Hoshino T, Uchiyama Y, Takeuchi Y, Okazawa M, Sakakibara H (2009) A phase II study of S-1 monotherapy as second-line treatment for advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* **64**(6): 1181–1185.

Wakelee HA, Dahlberg SE, Keller SM, Gandara DR, Graziano SL, Leighl NB, Adjei AA, Schiller JH (2011) Interim report of on-study demographics and toxicity from E1505, a phase III randomized trial of adjuvant chemotherapy with or without bevacizumab for completely resected early-stage non-small cell lung cancer. *J Clin Oncol* **29**(15S): 456s.

Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, Fry W, Bethune D, Ayoub J, Ding K, Seymour L, Graham B, Tsao MS, Gandara D, Kesler K, Demmy T, Shepherd F (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* **352**(25): 2589–2597.

Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial

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Summary

Background **The primary analysis of the JGOG 3016 trial showed that a dose-dense paclitaxel and carboplatin regimen significantly improves progression-free and overall survival compared with the conventional regimen as first-line chemotherapy for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer. We report the long-term follow-up results for survival.**

Methods **This randomised controlled trial was done at 85 centres in Japan. Patients with stage II–IV ovarian cancer were randomly assigned to receive conventional treatment (carboplatin area under the curve [AUC] 6 mg/mL per min and paclitaxel 180 mg/m² on day 1) or dose-dense treatment (carboplatin AUC 6 mg/mL per min on day 1 and paclitaxel 80 mg/m² on days 1, 8, and 15). The treatments were repeated every 3 weeks for six cycles; responding patients had three additional cycles. The randomisation was done centrally by telephone or fax, stratified by residual disease, stage, and histological type. The primary endpoint was progression-free survival; overall survival was a secondary endpoint. Long-term information on adverse events was not collected. Efficacy analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00226915.**

Findings **637 patients were enrolled, of whom 631 were analysed (312 assigned to the dose-dense regimen, 319 to the conventional regimen). Median follow-up was 76·8 months (IQR 68·9–85·6). Median progression-free survival was significantly longer in the dose-dense treatment group than in the conventional treatment group (28·2 months [95% CI 22·3–33·8] *vs* 17·5 months [15·7–21·7]; hazard ratio [HR] 0·76, 95% CI 0·62–0·91; p=0·0037). Median overall survival was 100·5 months (95% CI 65·2–∞) in the dose-dense treatment group and 62·2 months (52·1–82·6) in the conventional treatment group (HR 0·79, 95% CI 0·63–0·99; p=0·039).**

Interpretation **Dose-dense treatment offers better survival than conventional treatment and is a potential new standard of care for first-line chemotherapy for patients with advanced epithelial ovarian cancer.**

Funding **Japanese Gynecologic Oncology Group, Bristol-Myers Squibb.**

Introduction

A combination of paclitaxel and carboplatin is the standard first-line chemotherapy regimen for treatment of ovarian cancer. In the most recent consensus statements for management of ovarian cancer[1] from the 4th International Ovarian Cancer Consensus Conference, the Gynecologic Cancer InterGroup recommended the use of paclitaxel 175 mg/m², administered intravenously over 3 h, followed by carboplatin as an intravenous infusion over 30–60 min at an area under the curve of 5–6 mg/mL per min repeated every 3 weeks for six cycles. Further treatment options recommended by the group include intraperitoneal treatment for patients with small-volume residual disease and dose-dense weekly paclitaxel in combination with carboplatin every 3 weeks. These recommendations were based on the results of JGOG 3016,[2] in which the Japanese Gynecologic Oncology Group showed that progression-free survival was significantly improved in patients taking dose-dense paclitaxel and carboplatin (28·0 months), compared with those taking conventional paclitaxel and carboplatin every 3 weeks (17·2 months), as a first-line chemotherapy regimen for stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer (hazard ratio [HR] 0·71, 95% CI 0·58–0·88; log-rank p=0·0015).

Dose-dense paclitaxel and carboplatin prolonged progression-free survival by 11 months in the primary analysis at a median follow-up of 29 months, despite a higher proportion of patients discontinuing treatment in the dose-dense paclitaxel and carboplatin group (53% *vs* 37%).[2] Overall survival at 3 years was 72·1% in the dose-dense group and 65·1% in the conventional group (HR 0·75, 95% CI 0·57–0·98; p=0·03). Severe haematological and non-haematological toxic effects, including

neuropathy, were much the same between groups except for anaemia, which was significantly more common in the dose-dense paclitaxel and carboplatin group. Here, we report the long-term follow-up results for progression-free and overall survival from a post-hoc analysis.

Methods

Participants

JGOG 3016 was a randomised, controlled trial[2]—details of the study have been published previously. The study was done in 85 centres in Japan. Patients with histologically identified stage II–IV epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer were eligible. If the results of only cytological examinations were available, patients had to meet the following criteria: (1) a cytological diagnosis of adenocarcinoma, (2) an abdominal mass more than 2 cm in diameter on abdominal images, and (3) a CA125:carcinoembryonic antigen (CEA) ratio[3] of more than 1:25 or no evidence of gastrointestinal cancer if the CA125:CEA ratio was less than or equal to 1:25. Patients also had to be aged 20 years or older, have an Eastern Cooperative Oncology Group performance status of 0–3, and have adequate organ function. Patients were excluded if they had an ovarian tumour with a low malignant potential or a synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ.

All patients gave written informed consent before enrolment. The study was approved by the institutional review boards of all participating centres.

Randomisation and masking

We did randomisation centrally by telephone or fax, stratified by residual disease (≤1 cm *vs* >1 cm), International Federation of Gynecology and Obstetrics stage (stage II *vs* stage III *vs* stage IV), and histological type (clear-cell or mucinous *vs* serous or other) with an option to avoid imbalances greater than two within each institution. The randomisation sequence was generated by an independent registration office using a validated computer system. The trial was open-label.

Procedures

Patients were randomly assigned to receive paclitaxel and carboplatin as either a conventional regimen or a dose-dense regimen. Both groups received carboplatin at a dose calculated to produce an area under the curve (AUC) of 6 mg/mL per min on day 1 of a 21-day cycle, given as an intravenous infusion over 1 h. Patients given the conventional regimen also received paclitaxel, 180 mg/m² on day 1, given as a 3 h intravenous infusion. In the dose-dense group, paclitaxel was given as a 1 h intravenous infusion at a dose of 80 mg/m² on days 1, 8, and 15. The dose of carboplatin was calculated with the formula of Calvert using creatinine clearance instead of the glomerular filtration rate. Creatinine clearance was calculated with the formula of Jelliffe.[4] Irrespective of the calculated doses, the maximum absolute dose given to each patient was limited to 1000 mg. Treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or a complete response received three additional cycles of chemotherapy.

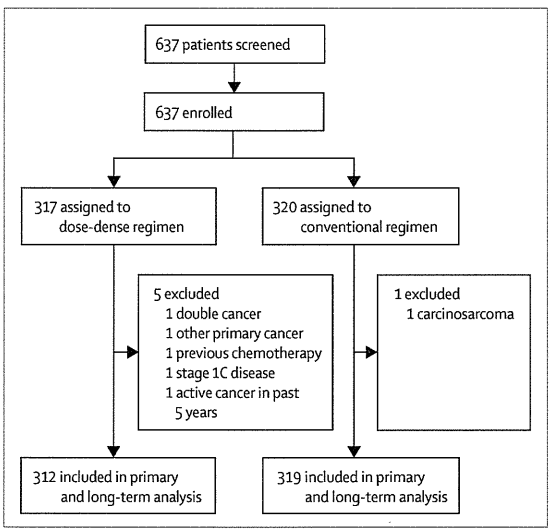

Figure 1: **Trial profile**

Patients in both groups had to have an absolute neutrophil count of 1000 cells per μL or greater and a platelet count of 75 000 platelets per μL or greater to receive subsequent cycles of treatment. Patients taking the dose-dense regimen also had to have an absolute neutrophil count of 500 cells per μL or greater and a platelet count of 50 000 platelets per μL or greater before they received paclitaxel on days 8 and 15. Treatment was delayed for a maximum of 3 weeks. The carboplatin dose was reduced when febrile neutropenia occurred, an absolute neutrophil count of less than 500 cells per μL persisted for 7 days or longer, platelet count was less than 10 000 platelets per μL, platelet count was 10 000–50 000 platelets per μL accompanied by signs of bleeding, or treatment was delayed because of haematological toxic effects for more than 1 week. The dose of paclitaxel was reduced in patients with grade 2 or higher peripheral neuropathy. Patients could have interval debulking surgery after two to four cycles of chemotherapy, secondary debulking or second-look surgery after six cycles of chemotherapy, or both.

Radiological studies to assess the status of all measurable lesions noted at baseline were repeated after two, four, and six cycles of chemotherapy. After patients discontinued the protocol treatment, disease status was assessed every 3 months for the first 2 years and every 6 months thereafter. Follow-up monitoring included clinical examinations and estimation of CA125 concentration; routine CT scans were not necessary but were requested if the CA125 concentration increased or symptoms of relapse developed.

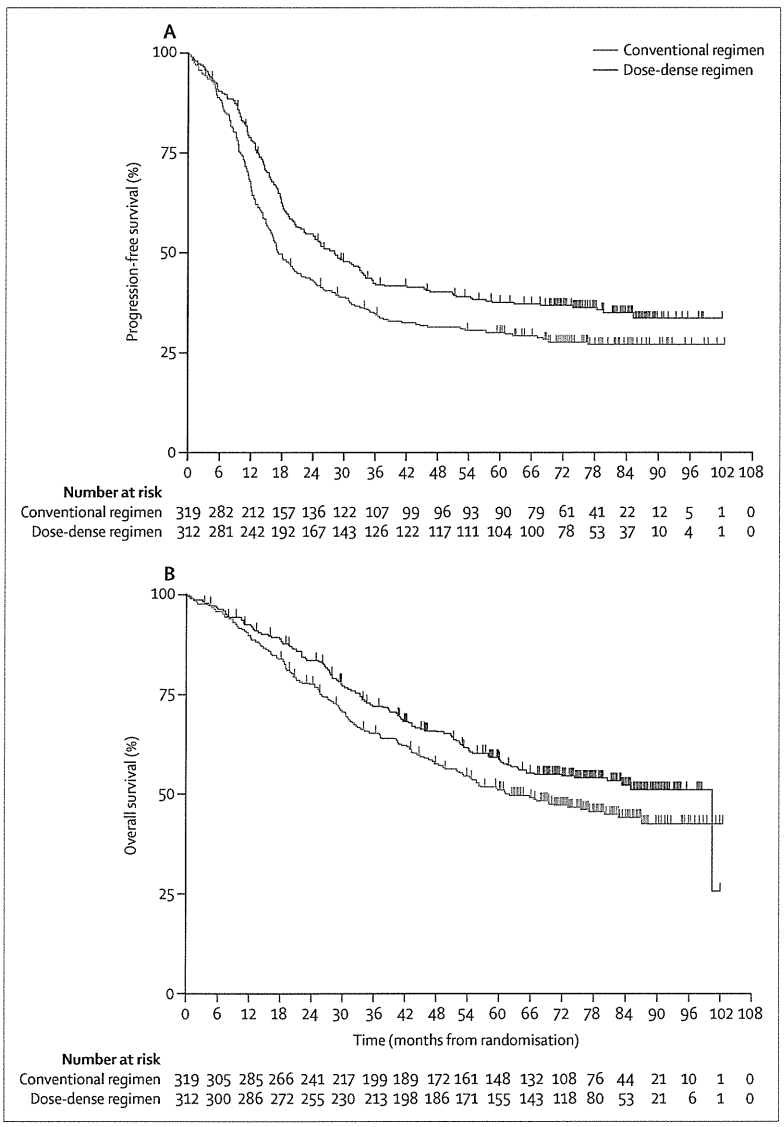

Figure 2: **Kaplan-Meier analyses of survival by treatment regimen**
Progression-free survival (A) and overall survival (B) in each treatment group.

The primary endpoint was progression-free survival, secondary endpoints were overall survival, response rate, and adverse events. In the present analysis we assessed long-term progression-free survival and overall survival. Long-term information on adverse events was not collected.

Statistical analysis

This post-hoc analysis of the trial was triggered after a median of more than 5 years' follow-up in the surviving patients, with a data cutoff date of Oct 31, 2011. The planned analyses of progression-free survival and overall survival included data on eligible patients according to the intention-to-treat principle. Progression-free survival was defined as the time from the date of randomisation to the date of the first occurrence of any of: death from any cause, appearance of any new lesions that could be measured or assessed clinically, or meeting the CA125 criteria for disease progression.[5] Overall survival was defined as the time from the date of randomisation to the date of death resulting from any cause. In January, 2005, the protocol was amended to have a sample size of 600 patients. This sample size would enable the detection of a 31·3% improvement (from 16 months to 21 months) in median progression-free survival with 80% power, two-sided log-rank test, at an alpha level of 0·05, an accrual of 3 years, and a follow-up of 1·5 years.

We evaluated survival by the Kaplan-Meier method, and compared treatment groups with the log-rank test. We used a Cox proportional hazards model to calculate HRs and 95% CIs. We also used a Cox proportional hazards model to assess the effect of treatment after adjustment for histological subtypes, residual disease, and performance status. Subgroup analyses included a log-rank test stratified for factors used for randomisation and interaction analyses based on stratification factors. All the analyses were done with SAS software (version 9.2).

This study is registered with ClinicalTrials.gov, number NCT00226915.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. NK, FT, and HM had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 28, 2003 and Dec 28, 2005, 637 patients were enrolled. 631 patients (312 patients in the dose-dense regimen group and 319 patients in the conventional regimen group) were evaluable in the analysis of long-term outcomes (figure 1).

At the time of the final follow-up (Oct 31, 2011), median follow-up was 76·8 months (IQR 68·9–85·6) for patients with censored data. 426 patients had progressed or died and 307 deaths had been recorded.

Both progression-free survival and overall survival were significantly longer in the dose-dense regimen group than in the conventional regimen group (figure 2). Median progression-free survival was 28·2 months (95% CI 22·3–33·8) in the dose-dense regimen group and 17·5 months (15·7–21·7) in the conventional regimen group (HR 0·76, 95% CI 0·62–0·91; p=0·0037). Median overall survival was 100·5 months (95% CI 65·2–∞) in the dose-dense regimen group versus 62·2 months (52·1–82·6) in the conventional regimen group (HR 0·79, 95% CI 0·63–0·99; p=0·039). 5-year overall survival was 58·7%

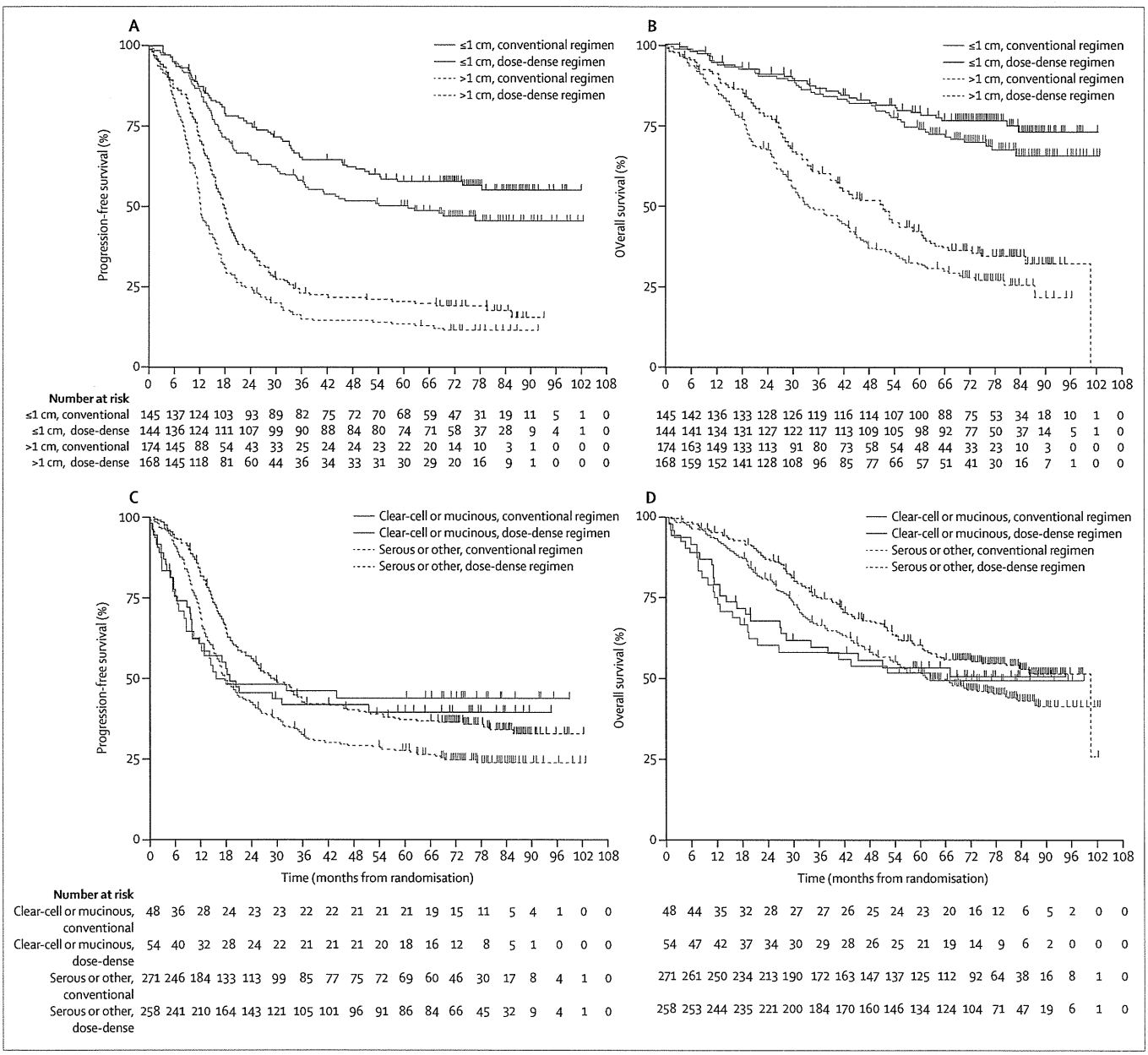

Figure 3: **Kaplan-Meier analyses of survival by treatment regimen in subgroups**
Progression-free survival (A) and overall survival (B) in each treatment group, stratified by residual disease (≤1 cm *vs* >1 cm), and progression-free survival (C) and overall survival (D) in each treatment group, stratified by histological type.

(95% CI 52·9–64·1) in the dose-dense group versus 51·1% (45·4–56·6) in the conventional regimen group.

Figure 3 and the appendix show survival by the stratification subgroups. Median progression-free survival in patients with residual disease at least 1 cm was higher for those dose-dense regimen group than for those in the conventional regimen group (17·6 months, 95% CI 15·6–19·4 *vs* 12·1 months, 11·2–14·3; HR 0·71, 95% CI 0·56–0·89; p=0·0029; figure 3A). Median progression-free survival in patients with residual disease less than 1 cm tended did not differ significantly between groups (not reached *vs* 60·9 months, 35·0–∞; HR 0·74, 95% CI 0·53–1·04; p=0·08; figure 3A). Median overall survival of patients with residual disease at least 1 cm was better in the dose-dense regimen group versus the conventional regimen group (51·2 months,

	Progression-free survival		Overall survival	
	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Conventional regimen *vs* dose-dense regimen	0·72 (0·60–0·88)	0·0009	0·79 (0·63–0·99)	0·0403
Stage				
II *vs* III	3·33 (2·24–4·94)	<0·0001	3·24 (1·92–5·47)	<0·0001
II *vs* IV	4·49 (2·86–7·06)	<0·0001	4·27 (2·40–7·59)	<0·0001
Residual disease (≤1 cm *vs* >1 cm)	2·17 (1·75–2·71)	<0·0001	2·58 (1·96–3·39)	<0·0001
Performance status (0–1 *vs* 2–3)	1·50 (1·11–2·03)	0·0085	1·70 (1·23–2·35)	0·0015

HR=hazard ratio.

Table: **Results of multivariate analysis for progression-free survival and overall survival**

40·1–58·3 *vs* 33·5 months, 29·3–43·6; HR 0·75, 95% CI 0·57–0·97; p=0·0027; figure 3B), but it did not differ significantly between treatment groups in patients with residual disease less than 1 cm (not reached *vs* not reached; HR 0·76, 95% CI 0·49–1·19; p=0·23; figure 3B). According to histological subtype, progression-free and overall survival of patients with serous or other histological subtypes was longer in the dose-dense regimen group than in the conventional regimen group (median progression-free survival 28·7 months, 95% CI 24·0–35·3 *vs* 17·5 months, 15·8–21·1; HR 0·70, 95% CI 0·57–0·86; p=0·0007; median overall survival 100·5 months, 65·2–∞ *vs* 61·2 months, 52·6–82·6; HR 0·76, 95% CI 0·59–0·97; p=0·0252; figure 3C, 3D). In patients with clear-cell or mucinous tumours, progression-free and overall survival did not differ significantly between treatment groups (median progression-free survival 18·7 months, 9·9–∞ *vs* 16·7 months, 8·5–∞; HR 1·06, 95% CI 0·63–1·76; p=0·84; median overall survival not reached *vs* 62·2 months, 19·0–∞; HR 0·92, 95% CI 0·53–1·61; p=0·776; figure 3C, 3D).

In the multivariate analysis, after adjustment for prognostic variables, treatment with the dose-dense regimen was associated with a significantly better progression-free and overall survival (table). Stage III or IV disease, residual disease at least 1 cm, and a poor performance status were associated with poor progression-free survival and overall survival (table). We did ad-hoc analyses to assess the effect of treatment delays, dose reductions, and dose intensity of carboplatin and paclitaxel. Dose reductions, treatment delays of chemotherapy, or lower relative dose intensity (<80%) of carboplatin were not independent prognostic factors for overall survival (data not shown). Only lower relative dose intensity (<80%) of paclitaxel was associated with a poor overall survival (HR 1·42, 95% CI 1·12–1·81; p=0·004) according to multivariate analysis.

Discussion

A combination of platinum and a taxane has been a cornerstone of treatment of epithelial ovarian, fallopian tube, and peritoneal cancer for more than 15 years. The addition of a third cytotoxic drug provides no benefit, including in both triplet combinations and sequential doublets.[6] However, improvements might be made through changes in scheduling, dose intensity, or delivery.[7] We have shown that a dose-dense regimen improves progression-free and overall survival after 5 years of follow-up. The long-term results of this study, in which each group received the same dose and schedule of carboplatin, reinforce this strategy as a potential standard of care (panel).

We did not assess long-term adverse events in the present study. In the original report,[2] anaemia was more common in the dose-dense regimen group versus the conventional regimen group (69% *vs* 44%), but other haematological toxic effects, grade 3 or 4 hypersensitivity reactions (1·9% *vs* 1·6%), and neurotoxicity (7% *vs* 6%) were not significantly different between groups.

Median overall survival in the optimally resected group (with residual disease <1 cm) who received the conventional regimen was better than that in previous trials done in Europe and the USA. This and other studies have shown that Asian patients with ovarian cancer have significantly better survival than do non-Hispanic white patients.[9,10] The study by duPont and colleagues[9] enrolled patients from South Korea and Japan in the Gynecologic Oncology Group 218 phase 3 study with advanced-stage ovarian cancer.[8] Overall survival was significantly higher in Asian patients when adjusted for age, stage, residual disease, performance status, and histology. Future studies should explore biological differences, environmental factors, socioeconomic factors, and response to treatment to clarify the racial and ethnic differences in survival.

In the stratification subgroup analyses, the greatest benefit was achieved in the group of patients with residual disease of 1 cm or more and who had serous or other histology (not clear-cell or mucinous). The improvement in median overall survival (33·5 to 51·2 months) was greater than the improvement in median progression-free survival (12·1 to 17·6 months) for patients with residual disease of 1 cm or more. The reason for this difference is unclear, although subsequent treatment could affect this outcome. The proportion of patients who received subsequent treatments (chemotherapy including platinum *vs* non-platinum chemotherapy) after discontinuation of the protocol treatment did not differ between both groups (data was not shown). However, we did not assess the patients who received subsequent treatment with weekly paclitaxel. The dose-dense regimen might have had a favourable effect in the optimally resected group: progression-free survival was longer in this group. More patients or more events will be needed to detect the effect on overall survival. We report no advantage for clear cell or mucinous histological types, suggesting that other

Panel: Research in context

Systematic review

We searched PubMed, the abstracts of major oncology congresses (American Society of Clinical Oncology and European Society for Medical Oncology), and ClinicalTrials.gov. We used MeSH and full-text search terms for advanced ovarian cancer, chemotherapy, and phase 3 clinical trials, limiting our results to English language articles and abstracts published or presented in the past 2 years. For PubMed, the search was: (advanced[All Fields] AND ("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields])) AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields]) AND (Clinical Trial, Phase III[ptyp] AND ("2010/07/05"[PDAT] : "2013/07/05"[PDAT]) AND English[lang]). For conferences, the search was: "ovarian cancer" or "advanced ovarian cancer", manually limited to abstracts. The last search was done on July 5, 2013. We identified 14 results in PubMed. The most promising treatment was bevacizumab[8] combined with first-line chemotherapy of carboplatin and paclitaxel for advanced ovarian cancer. The use of bevacizumab during and up to 10 months after carboplatin and paclitaxel chemotherapy prolongs median progression-free survival by about 4 months.

Interpretation

Dose-dense carboplatin and paclitaxel is the most active treatment other than targeted treatment with bevacizumab for advanced ovarian cancer. Several confirmatory trials using the dose-dense regimen with or without bevacizumab are now ongoing in Europe and the USA. If these studies confirm the results of JGOG 3016, then it is likely that dose-dense chemotherapy will become an internationally accepted standard of care.

treatment strategies are needed. Both clear cell and mucinous tumours are distinct from high-grade serous cancer and can be classified as type I ovarian cancers, whereas type II tumours comprise the more common high-grade serous carcinomas.[11] A randomised clinical trial (JGOG 3017; University Hospital Medical Information Network in Japan number 000000499) is underway to compare carboplatin and paclitaxel with cisplatin and irinotecan. Standard chemotherapeutic drugs have only modest activity against clear-cell cancer. Greater benefits might be achieved with molecularly targeted treatments, such as sunitinib[12] or mTOR inhibitor.[13]

We calculated the carboplatin dose with the formulas of Calvert and Jellife without adjustment for serum creatinine concentrations. We used the enzymatic peroxidase-antiperoxidase method to estimate the glomerular filtration rate for measurement of serum creatinine. This method can result in an excessive dose of carboplatin and more severe myelotoxicities than the methods used in previous trials.[6,14] Several methods have been proposed to estimate the glomerular filtration rate more accurately,[15–17] but no global consensus exists as to the best method for assessment of renal function as the basis for determining the dose of carboplatin. For this reason, we did not use any adjustment methods to calculate the carboplatin dose. In our post-hoc prognostic analysis, the relative dose intensity of carboplatin was not associated with progression-free or overall survival (data not shown). Therefore, possible excessive doses of carboplatin probably have little effect on survival compared with the different dose schedules for paclitaxel.

The best doses and schedule for a dose-dense regimen of paclitaxel and carboplatin are still unclear. An Italian trial (MITO-7; NCT00660842) is assessing a different schedule of weekly carboplatin and a lower paclitaxel dose than our trial: weekly carboplatin (AUC 2 mg/mL per min) plus weekly paclitaxel (60 mg/m²) compared with carboplatin (AUC 6 mg/mL per min, administered every 3 weeks) and paclitaxel (175 mg/m²). The weekly regimen did not significantly improve progression-free survival compared with the conventional regimen (18·8 months *vs* 16·5 months; p=0·18), but was associated with better quality of life and fewer toxic effects.[18] Other ongoing studies—including the ICON8 trial (NCT01654146), the GOG 262 trial (NCT01167712), and the GOG 262 trial (NCT00951496)—are assessing different schedules and doses in an effort to establish the best dose-dense regimen.

Dose-dense treatment offers a potential new standard of care for first-line chemotherapy for patients with advanced epithelial ovarian cancer. Ongoing studies will clarify the best dose, schedule, and route of administration.

Contributors

NK, MY, SI, FT, HM, EK, TS, and KO had the idea for, and designed, the study with the Japanese Gynecologic Oncology Group. MY was the coordinating principal investigator. NK, FT, and HM analysed and interpreted the results. NK wrote the first draft. KO was responsible for the overall planning and conduct of the study. NK, MY, SI, EK, DA, TJ, SK, FT, TS, and KO enrolled patients and collected data. NK, MY, TS, EK, and KO were members of the steering committee. All authors were involved in writing the report and approved the final version of the manuscript.

Conflicts of interest

SI has received honoraria from Bristol-Myers Squibb. NK has received honorara from Nippon Kayaku. NK and DA have received grants from Nippon Kayaku. The other authors declare that they have no conflicts of interest.

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References

1 Thigpen T, Dubois A, McAlpine J, et al. First-line therapy in ovarian cancer trials. *Int J Gynecol Cancer* 2011; **21**: 756–62.

2 Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009; **374**: 1331–38.

3 Yedema CA, Kenemans P, Wobbes T, et al. Use of serum tumor markers in the differential diagnosis between ovarian and colorectal adenocarcinomas. *Tumour Biol* 1992; **13**: 18–26.

4 Jelliffe RW. Letter: creatinine clearance: bedside estimate. *Ann Intern Med* 1973; **79**: 604–05.

5 Rustin GJ, Timmers P, Nelstrop A, et al. Comparison of CA-125 and standard definitions of progression of ovarian cancer in the intergroup trial of cisplatin and paclitaxel versus cisplatin and cyclophosphamide. *J Clin Oncol* 2006; **24**: 45–51.

6 Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol* 2009; **27**: 1419–25.

7 Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev* 2011; **11**: CD005340.

8 Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011; **365**: 2473–83.

9 duPont NC, Brady MF, Burger RA, et al. Prognostic significance of ethnicity and age in advanced stage ovarian cancer: an analysis of GOG 218. SGO Annual Meeting. 2013; abstract 54.

10 Fuh K, Shin J, Blansit K, et al. The treatment and survival differences of Asians versus whites with epithelial ovarian cancer. SGO Annual Meeting. 2013; abstract 53.

11 Kurman RJ, Shih Ie M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol* 2010; **34**: 433–43.

12 Anglesio MS, George J, Kulbe H, et al. IL6-STAT3-HIF signaling and therapeutic response to the angiogenesis inhibitor sunitinib in ovarian clear cell cancer. *Clin Cancer Res* 2011; **17**: 2538–48.

13 Behbakht K, Sill MW, Darcy KM, et al. Phase II trial of the mTOR inhibitor, temsirolimus and evaluation of circulating tumor cells and tumor biomarkers in persistent and recurrent epithelial ovarian and primary peritoneal malignancies: a Gynecologic Oncology Group study. *Gynecol Oncol* 2011; **123**: 19–26.

14 du Bois A, Luck HJ, Meier W, 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**: 1320–29.

15 Ando M, Minami H, Ando Y, et al. Multi-institutional validation study of carboplatin dosing formula using adjusted serum creatinine level. *Clin Cancer Res* 2000; **6**: 4733–38.

16 Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247–54.

17 Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–92.

18 Pignata S, Scambia G, Lauria R, et al. A randomized multicenter phase III study comparing weekly versus every 3 weeks carboplatin (C) plus paclitaxel (P) in patients with advanced ovarian cancer (AOC): Multicenter Italian Trials in Ovarian Cancer (MITO-7)—European Network of Gynaecological Oncological Trial Groups (ENGOT-ov-10) and Gynecologic Cancer Intergroup (GCIG) trial. *Proc Am Soc Clin Oncol* 2013; **31** (suppl): abstr LBA5501.

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Feasibility study of paclitaxel plus carboplatin in patients with endometrial cancer: A Japan Kanto Tumor Board study (JKTB trial)

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Abstract

Aim: The optimal chemotherapy regimen for patients with endometrial cancer has not been established. We assessed the feasibility of paclitaxel plus carboplatin (TC) for postoperative chemotherapy in patients with endometrial cancer.

Material and Methods: Patients with newly diagnosed endometrial cancer received TC (paclitaxel 180 mg/m^2, carboplatin AUC6 mg/mL/min) every three weeks. Treatment was continued until disease progression or completion of six cycles. Toxicities were evaluated every cycle according to NCI-CTCAE version 3.0.

Results: Sixty patients were registered from December 2005 through November 2006. Forty-four of 60 (73.3%) cases completed all of the planned six cycles. Grades 3 and 4 hematologic toxicities were observed as follows: leukopenia (61.7%), neutropenia (95.0%), anemia (21.7%), and thrombocytopenia (5.0%). There were six patients who dropped out from the protocol by neutropenia. Grade 3 non-hematologic toxicities were observed as follows: nausea (3.3%), vomiting (1.7%), neuropathy (5.0%), myalgia (6.7%) and constipation (1.7%). No grade 4 non-hematologic toxicity was observed.

Conclusion: This TC regimen is feasible for endometrial cancer patients.

Key words: endometrial cancer, feasibility, paclitaxel/carboplatin, postoperative chemotherapy.

Introduction

Endometrial cancer is one of the most common gynecologic malignancies in Japan, and its incidence has been increasing recently.[1] Endometrial cancer in general is considered to have relatively good prognosis. However, the five-year survival rates for stage III and IV are 61.9% and 21.1%, respectively,[2] and patients at advanced stage have poor prognosis. To treat endometrial cancer, surgery, chemotherapy, radiation, and hormone therapy are used either alone or sequentially. Surgery is the foundation of the management of patients with endometrial cancer. However, there are differences in adjuvant therapies between Japan and Western countries; chemotherapy is used more often in Japan.

To establish the standard treatment for endometrial cancer in Japan, the first guideline for the treatment of

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