limited,[4-14] and each study included fewer than 60 patients, too small a population to allow consensus regarding recommendations for patient selection for fertility-sparing surgery in stage I EOC. This study attempted to determine selection criteria for fertility-sparing surgery in stage I EOC patients on the basis of clinical outcomes for more than 200 stage I EOC patients who underwent fertility-sparing surgery.

PATIENTS AND METHODS

Patients

Between 1985 and 2004, patients with stage I invasive EOC who underwent fertility-sparing surgery in 30 institutions belonging to the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group or who were referred to these hospitals immediately after fertility-sparing surgery performed elsewhere were enrolled onto this study. Patients were eligible if they had stage I, G1, G2, or G3 EOC; if they were treated using fertility-sparing surgery (conservation of the uterus and contralateral ovary and fallopian tube); and if they were ≤ 40 years of age at the time of fertility-sparing surgery. Four patients (stage IB, n = 2; stage IC, n = 2) who showed microscopic metastases in biopsy specimens from the opposite ovary were excluded from this study because of the small number of patients and the insufficient durations of follow-up.

Reassessment of histologic cell type and tumor differentiation was performed in each institution according the WHO criteria before enrollment onto the present study. Histologic differentiation was defined as G1, well differentiated; G2, moderately differentiated; or G3, poorly differentiated. Staging was determined according to the International Federation of Gynecology and Obstetrics (FIGO) classification (1987). In this study, stage IC patients were classified into three subgroups: stage IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule rupture and/or tumor on ovarian surface with negative peritoneal cytology; and IC(1/2), malignant cells in ascites or peritoneal washings. Institutional review board approval was obtained from each institution before initiating this investigation.

Factors for Analysis

Mucinous, serous, endometrioid, and mixed epithelial adenocarcinoma were classified by histologic grade (G1, G2, or G3). Clear cell histology was not graded in this study. We defined G1/2 non-clear cell adenocarcinoma as showing favorable histology.

Stage IA or IC patients with unilateral ovarian involvement were divided into six subgroups to determine patient selection for fertility-sparing surgery, as follows: stage IA and favorable histology, stage IA and clear cell histology, stage IA and G3, stage IC and favorable histology, stage IC and clear cell histology, or stage IC and G3.

We defined lethal recurrence (LR) as recurrence showing lesions outside the remaining ovary, because a considerable number of previous reports[15] have suggested that patients with recurrence exclusively within the remaining ovary show much better prognosis following salvage surgery compared with patients displaying other patterns of recurrence. Outcomes for patients were analyzed using overall survival (OS), recurrence-free survival (RFS), and lethal recurrence–free survival (LRFS). We also investigated reproductive outcomes after fertility-sparing surgery in patients who provided the information.

Statistical Analysis

Statistical analysis of data was performed using the JMP Statistics package (SAS Institute, Cary, NC). Two-sided probability values were calculated throughout and considered to be significant at the level of $P < .05$. Survival estimates were generated using Kaplan-Meier methods. Differences between groups were tested using log-rank testing.

RESULTS

Patient Characteristics

A total of 211 patients with unilateral stage I EOC (stage IA, n = 126; stage IC, n = 85) were entered onto the study. Table 1 summarizes the main characteristics of patients and tumors. Mean patient age was 29 years (range, 14 to 40 years). Median duration of follow-up after excluding patients who died was 78 months from initial fertility-sparing surgery (range, 3 to 270 months).

Surgical Treatments

Of the 211 patients, 23 (10.9%) patients underwent restaging laparotomy because of inadequate staging or cytoreduction at initial surgery. Nine of the 23 patients underwent unilateral ovarian cystectomy at initial surgery (laparoscopy, n = 4; laparotomy, n = 5) and unilateral salpingo-oophorectomy at restaging laparotomy. As a result, 205 patients underwent unilateral salpingo-oophorectomy. The

Table 1. Patient Characteristics (N = 211)

Characteristic	No.	%
Age, years		
Median	29	
Range	14-40	
Parity		
Parous	26	12.3
Nulliparous	185	87.7
FIGO stage		
IA	126	59.7
IC	85	40.3
Substage		
IC(b)	55	26.1
IC(a)	18	8.5
IC(1/2)	12	5.7
Cell type		
Mucinous	126	59.7
Serous	27	12.8
Endometrioid	27	12.8
Clear cell	30	14.2
Mixed epithelial	1	0.5
Histologic differentiation		
Well (G1)	160	75.8
Moderate (G2)	15	7.1
Poor (G3)	6	2.8
Not classified (clear cell)	30	14.2
FIGO stage and histologic differentiation		
IA		
G1	95	47.3
G2	13	6.2
G3	3	1.4
Clear cell	15	7.1
IC		
G1	65	30.8
G2	2	0.9
G3	3	1.4
Clear cell	15	7.1

Abbreviations: G(1/2/3), non-clear cell histology grade (1/2/3); FIGO, International Federation of Gynecology and Obstetrics; IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule ruptured and/or tumor on ovarian surface with negative peritoneal cytology; IC(1/2), malignant cells in ascites or peritoneal washings.

Table 2. Types of Surgery in Initial Treatment

Surgery Type	No. of Patients
Unilateral salpingo-oophorectomy	205
Alone	64
BO	43
OM	16
RLND	5
BO + OM	27
BO + RLND	5
OM + RLND	18
BO + OM + RLND	26
Unknown	1
Unilateral ovarian cystectomy	6
BO	3
RLND	1
BO + OM	1
Unknown	1

Abbreviations: BO, biopsy from the opposite ovary; OM, partial omentectomy; RLND, retroperitoneal lymph node dissection or biopsy.

remaining six patients underwent unilateral ovarian cystectomy at initial laparotomy, not followed by restaging surgery. As for other surgeries, 105 patients underwent biopsy (wedge resection) of the opposite ovary, 88 patients underwent partial omentectomy, and 55 patients underwent retroperitoneal lymph node dissection or biopsies. Table 2 provides details of surgical treatments.

Surgical staging included careful inspection and palpation of peritoneal surfaces with biopsies of any suspect lesions and peritoneal washing cytology. No patients received endometrial curettage during surgery, although most patients had endometrial cytology or biopsy before surgery. If optimal surgical staging required at least omentectomy in addition to unilateral salpingo-oophorectomy, 87 (41.2%) of the 211 patients were optimally staged and 124 (58.8%) were nonoptimally staged. Only 74 (35.1%) patients were optimally staged in one-step surgery.

Adjuvant Chemotherapy

Platinum-based adjuvant chemotherapy was administered to 125 (59.2%) patients, with a mean number of four cycles (range, 1 to 12 cycles). The most common chemotherapy regimens were cisplatin + cyclophosphamide ± doxorubicin (57 of 125; 45.6%) and carboplatin + paclitaxel (46 of 125; 36.8%). Fifteen (7.1%) patients received adjuvant chemotherapy without platinum (including oral medication). The remaining 71 (33.6%) patients received no adjuvant treatment after initial surgery.

Clinical Outcomes

Recurrence was identified during the follow-up period for 18 (8.5%) of 211 patients. Of these 18 patients, five showed recurrence exclusively in the remaining ovary (non-LR; Table 3) and 13 had LR in sites other than the remaining ovary (Table 4). At the end of this investigation, eight patients were alive with no evidence of disease, five patients were alive with disease, and five patients had died of disease. All five patients with non-LR were treated with salvage surgery and showed no evidence of disease.

Stage IA and favorable histology. This subgroup included 108 stage IA patients with favorable histology. Of these, 44 (40.7%) patients received platinum-based adjuvant chemotherapy after surgery, and the 5-year OS, RFS, and LRFS were 100%, 97.8%, and 99.1%, respectively. Three patients with mucinous histology G1 developed LR at 14, 70, and 73 months after fertility-sparing surgery (Table 4). Median duration of follow-up for this group was 79 months.

Stage IA and clear cell histology. This subgroup included 15 stage IA patients with clear cell histology. Of those, nine (60%) patients were treated with platinum-based adjuvant chemotherapy. The 15 patients showed rates of 100% for 5-year OS, RFS, and LRFS. Median duration of follow-up for these patients was 78 months.

Stage IA and G3. One of the three stage IA patients with G3 received platinum-based adjuvant chemotherapy and was alive without recurrence 256 months after fertility-sparing surgery. Two patients without any adjuvant chemotherapy had LR at 25 and 31 months after fertility-sparing surgery (Table 4), although both were alive with disease at the end of this investigation (duration of follow-up, 65 and 90 months).

Stage IC and favorable histology. This subgroup included 67 stage IC patients with favorable histology. Platinum-based adjuvant chemotherapy was administered to 57 (85.1%) patients following surgery. The 5-year OS, RFS, and LRFS were 96.9%, 92.1%, and 95.4%, respectively. As for subgroups of stage IC [IC(b), n = 43; IC(a), n = 14; IC(1/2), n = 10], the 5-year RFS was 92.9%, 91.7%, and 90.0%, respectively. Three (4.5%) of 67 patients developed LR, with one stage IC(b) patient with endometrioid histology G1, one stage IC(b) patient with mucinous histology G1, and one IC(1/2) patient with serous histology G1 developing LR at 20, 8, and 3 months after fertility-sparing surgery, respectively (Table 4). Median duration of follow-up for this group was 76.5 months.

Table 3. Characteristics of Patients With Recurrence in the Residual Ovary Alone (non-lethal recurrence)

Patient No.	Age (years)	Stage	Histologic Type	Grade	Platinum-Based Chemotherapy	Time to Recurrence (months)	Follow-Up After Recurrence (months)	Status
1	18	IA	Mucinous	1	No	183	19	NED
2	26	IA	Serous	1	Yes	52	164	NED
3	26	IC(b)	Endometrioid	1	No	20	45	NED
4	36	IC(b)	Clear cell	Not graded	No	21	124	NED
5	26	IC(a)	Mucinous	1	Yes	43	6	NED

Abbreviations: NED, no evidence of disease; IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule ruptured and/or tumor on ovarian surface with negative peritoneal cytology.

Table 4. Characteristics of Patients Showing Recurrence With Lesions Outside the Residual Ovary (lethal recurrence)

Patient No.	Age (years)	Stage	Histologic Type	Grade	Platinum-Based Chemotherapy	Site of Recurrence	Time to Recurrence (months)	Follow-Up After Recurrence (months)	Status
1	19	IA	Mucinous	1	No	Peritoneum	70	149	NED
2	27	IA	Mucinous	1	No	Lung	73	34	DOD
3	29	IA	Mucinous	1	No	Abdominal wall	14	39	AWD
4	22	IA	Serous	3	No	Residual ovary, ascites	25	231	NED
5	40	IA	Endometrioid	3	No	Para-aortic lymph nodes	31	34	NED
6	15	IC(b)	Mucinous	1	Yes	Peritoneum	8	18	AWD
7	31	IC(b)	Endometrioid	1	Yes	Liver	20	6	DOD
8	29	IC(b)	Clear cell	Not graded	No	Para-aortic lymph nodes	15	86	AWD
9	29	IC(b)	Clear cell	Not graded	Yes	Residual ovary, ascites, peritoneum	11	197	DOD
10	36	IC(b)	Clear cell	Not graded	Yes	Liver	46	8	AWD
11	33	IC(a)	Endometrioid	3	Yes	Not recorded	5	5	DOD
12	26	IC(1/2)	Serous	1	Yes	Peritoneum	3	22	DOD
13	38	IC(1/2)	Clear cell	0	No	Residual ovary, pelvic lymph nodes, peritoneum	21	29	AWD

Abbreviations: NED, no evidence of disease; DOD, died of disease; AWD, alive with disease; IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule ruptured and/or tumor on ovarian surface with negative peritoneal cytology; IC(1/2), malignant cells in ascites or peritoneal washings.

Stage IC and clear cell histology. This subgroup included 15 stage IC patients with clear cell histology. Eleven (73.3%) of these patients were treated with platinum-based adjuvant chemotherapy. LR occurred in two patients with and in two patients without platinum-based adjuvant chemotherapy (Table 4). These 15 patients showed rates of 93.3%, 66.0%, and 72.7% for 5-year OS, RFS, and LRFS. In particular, 5-year RFS of 11 stage IC(b) patients resembled that of the other four stage IC patients (63.6% *v* 75.0%, respectively). Median duration of follow-up for the 14 survivors was 64 months.

Stage IC and G3. All three stage IC patients with G3 were treated using platinum-based chemotherapy after surgery, but one patient developed LR and died of disease 6 months after fertility-sparing surgery. The remaining two patients were alive without recurrence 58 and 230 months after fertility-sparing surgery.

Comparison of Clinical Outcomes Among Subgroups

We compared OS and RFS among the four subgroups except for the two subgroups (stage IA and G3, or stage IC and G3) consisting of only three patients. In terms of OS, no significant differences were seen among the four subgroups. Significant differences in RFS were seen between the following three pairs of subgroups: stage IA favorable histology versus stage IC clear cell histology (97.8% *v* 66.0%; $P < .001$), stage IC favorable histology versus stage IC clear cell histology (92.1% *v* 66.0%; $P = .008$), and stage IA clear cell histology versus stage IC clear cell histology (100% *v* 66.0%; $P = .02$).

Figure 1 shows OS and RFS curves in those with good prognosis (group I: stage IA favorable histology [n = 108]), those with fairly good prognosis (group II: stage IA clear cell histology or stage IC favorable histology [n = 82]), and those with poor prognosis (group III: stage IA G3, stage IC clear cell histology, or stage IC G3 [n = 21]). No significant differences in OS were seen between groups I and II ($P = .21$) or between groups II and III ($P = .29$), whereas significant differences were identified between groups I and III ($P = .02$). No significant differences in RFS were apparent between groups I and II ($P = .65$), but significant differences were noted between groups I and III ($P < .001$) and between groups II and III ($P < .001$).

Reproductive Outcomes

After fertility-sparing surgery with or without adjuvant chemotherapy, 182 (96.8%) of 188 patients who gave information on menstruation had almost the same cycle of menstruation as before treatment. Six (5.0%) of 121 patients who received platinum-based adjuvant chemotherapy showed continued secondary amenorrhea for 6, 48, 66, 72, 172, and 224 months following two to six cycles of chemotherapy (median, four cycles).

Of the 195 patients who gave reproductive outcomes at the end of the investigation, 55 (28.5%) patients achieved 76 pregnancies and 53 gave birth to 66 healthy children after fertility-sparing surgery. Five (9.1%) of 55 patients had received some kind of infertility treatment before pregnancy. These patients and their babies showed no clinical problems during the perinatal period. Four (9.4%) of 53 patients who gave birth to children underwent completion surgery, including hysterectomy and contralateral salpingo-oophorectomy, after childbearing.

Forty-five (53.6%) of 84 patients who were nulliparous at fertility-sparing surgery and married at the end of the follow-up period had achieved 65 pregnancies, and 43 had given birth to 56 healthy children during follow-up (mean follow-up, 8.8 years). Of the 84 patients, the remaining 39 patients had not conceived during follow-up (mean follow-up, 7.2 years), and mean age was 37 years (range, 25 to 54 years) at the end of the investigation.

DISCUSSION

In this series, recurrence rate among the 211 stage I EOC patients after fertility-sparing surgery was 8.5% (18 of 211), falling within the 5.4% to 30.3% reported previously.[5,6,10,12,14] Of the 18 patients with recurrence, five (2.4%) patients showing recurrence exclusively in the residual ovary achieved no evidence of disease. According to data from five studies[5,6,10,12,14] that investigated relationships between sites of recurrence and clinical outcomes, eight of 10 patients with recurrence limited to the residual ovary achieved no evidence of disease following salvage therapy, whereas only three of 21 patients with recurrence at

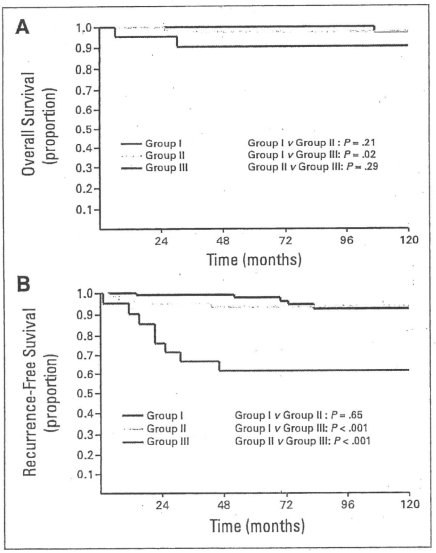

Fig 1. (A) Overall survival curves for patients with good prognosis (group I), fairly good prognosis (group II), and poor prognosis (group III). Group I: stage IA and favorable histology; group II: stage IA and clear cell histology, or stage IC and favorable histology; group III: stage IA and clear cell histology grade 3 (G3), stage IC and clear cell histology, or stage IC and G3. (B) Recurrence-free survival curves for groups I, II, and III.

extra-ovarian sites achieved no evidence of disease. We thus evaluated LRFS in addition to OS and RFS in this study.

The 108 stage IA patients with favorable histology showed a 5-year RFS of 97.8% and a 5-year LRFS of 99.1% (5-year recurrence rate, 2.2%; 5-year LR rate, 0.9%), although only 40.7% of these patients received platinum-based adjuvant chemotherapy after surgery. Stage IA patients with favorable histology were always included in selection criteria for fertility-sparing surgery in previous reports and in various guidelines.[1-14] The recurrence rate for stage IA patients with favorable histology in four previous reports[5,10,12,14] was 0% to 22.2% during follow-up. Our data confirm fertility-sparing surgery as a safe treatment option for stage IA patients with favorable histology, even when fertility-sparing surgery is not followed by adjuvant chemotherapy.

In this study, 15 stage IA patients with clear cell histology showed no recurrence, with lymph node biopsy or dissection performed in six (40%) patients and adjuvant platinum-based chemotherapy given to nine (60%) patients. Our data correspond with that in a recent report by Kajiyama et al[16] showing no recurrence in four stage IA patients with clear cell histology who had undergone fertility-sparing surgery. Other investigations,[10,12,14] however, have reported three recurrences among eight stage IA patients with clear cell histology after fertility-sparing surgery. These data suggest that stage IA patients with clear cell histology may be candidates for fertility-sparing surgery, including optimal staging followed by adjuvant chemotherapy.

In our series, only one of three stage IA patients with G3 survived for 5 years without recurrence. The recurrence rate for the 17 stage IA patients with G3 from six investigations[5,7,10-12,14] who underwent fertility-sparing surgery was 35.3% (6 of 17), although some reports classified clear cell histology into G3. These data suggest that fertility-sparing surgery cannot be recommended for stage IA patients with G3.

The 67 stage IC patients with favorable histology had a 5-year RFS of 92.1% and a 5-year LRFS of 95.5%. Outcomes seem to be better in our study compared with the recurrence rate of 12.8% (5 of 39) in previous studies.[7,10-12,14] Platinum-based adjuvant chemotherapy was more frequently given to this group compared with the stage IA and favorable histology group (85.1% *v* 40.7%; $P < .001$). In our series, no significant difference in 5-year RFS was seen among 43 IC(b) patients, 14 IC(a) patients, or 10 IC(1/2) patients with values of 92.9%, 91.7%, and 90.0%, respectively. Our data suggest that stage IC patients with favorable histology in the unilateral ovary can be candidates for fertility-sparing surgery, including optimal staging followed by adjuvant chemotherapy.

Our series included 15 stage IC patients with clear cell histology. These patients showed a 5-year RFS of 66.0% and a 5-year LRFS of 72.7%, even when 11 (73.3%) patients were treated with platinum-based adjuvant chemotherapy. Kajiyama[16] reported that one stage IC(2) patient among the six stage IC patients with clear cell histology experienced relapse and died of the disease. Five-year RFS was 63.6% for 11 IC(b) patients, 100% for two IC(a) patients, and 50% for two IC(1/2) patients. These data suggest that stage IC patients with clear cell histology cannot be candidates for fertility-sparing surgery.

Our series included three stage IC patients with G3. One patient developed LR and died of the disease 6 months after fertility-sparing surgery, although all three patients had been treated with platinum-based adjuvant chemotherapy. In previous reports,[10-14] four of nine stage IC patients with G3 who underwent fertility-sparing surgery displayed recurrence. These data suggest that fertility-sparing surgery cannot be recommended for stage IC patients with G3.

In addition to the study patients, during the study period, we managed four patients with unilateral stage I EOC treated with fertility-sparing surgery elsewhere, who were referred to these hospitals for treatment of lethal recurrent disease and died of the disease. These four patients included one stage IA patient with clear cell histology, one stage IA patient with G3, and two stage IC patients with G3. Clinical outcomes for these patients support our recommendations regarding fertility-sparing surgery for unilateral stage I EOC.

In our series, 5% of patients with platinum-based adjuvant chemotherapy developed secondary amenorrhea and infertility, suggesting that we should not administer adjuvant chemotherapy to patients with stage IA and favorable histology without serious consideration. As for the reproductive outcome, we confirmed that most married but nulliparous EOC patients undergoing fertility-sparing surgery can give birth to children within several years after fertility-sparing surgery.

In conclusion, this study confirmed that stage IA EOC patients with favorable histology can be safely treated with fertility-sparing surgery not followed by platinum-based adjuvant chemotherapy. We would thus propose that fertility-sparing surgery be considered

Table 5. Recommendation for Fertility-Sparing Surgery in Young Patients With Unilateral Stage I Ovarian Cancer

Stage	Histology/Grade		
	FH	CCH	G3
1A	Offer FSS	Consider FSS + CT	No FSS
1C	Consider FSS + CT	No FSS	No FSS

Abbreviations: FH, favorable histology (mucinous, serous, endometrioid, or mixed histology and grade 1 or 2); CCH, clear cell histology; G3, clear cell histology grade 3; FSS, fertility-sparing surgery; CT, adjuvant chemotherapy.

for stage IA EOC patients with clear cell histology and for stage IC EOC patients with unilateral ovarian involvement and favorable histology, under conditions of performing complete staging surgery and platinum-based adjuvant chemotherapy (Table 5). Conversely, fertility-sparing surgery cannot be recommended for patients with stage IA with G3 histology or stage IC with clear cell or G3 histology. Theoretically, a randomized controlled trial may be needed to compare conservative surgery with radical surgery for young patients with EOC to achieve high-quality evidence. However, such trials may not be ethically feasible. Confirming the decision of patient criteria for selection in a phase II trial would be appropriate.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Toyomi Satoh, Hiroyuki Yoshikawa
Administrative support: Toyomi Satoh
Provision of study materials or patients: Toyomi Satoh, Masayuki Hatae, Yoh Watanabe, Nobuo Yaegashi, Osamu Ishiko, Shoji Kodama, Satoshi Yamaguchi, Kazunori Ochiai, Masashi Takano, Harushige Yokota, Yosuke Kawakami, Sadako Nishimura, Daiki Ogishima, Shunsuke Nakagawa, Hiroaki Kobayashi, Tanri Shiozawa, Toru Nakanishi, Toshiharu Kamura, Ikuo Konishi
Collection and assembly of data: Toyomi Satoh, Masayuki Hatae, Yoh Watanabe, Nobuo Yaegashi, Osamu Ishiko, Shoji Kodama, Satoshi Yamaguchi, Kazunori Ochiai, Masashi Takano, Harushige Yokota, Yosuke Kawakami, Sadako Nishimura, Daiki Ogishima, Shunsuke Nakagawa, Hiroaki Kobayashi, Tanri Shiozawa, Toru Nakanishi
Data analysis and interpretation: Toyomi Satoh, Toshiharu Kamura, Ikuo Konishi, Hiroyuki Yoshikawa
Manuscript writing: Toyomi Satoh, Hiroyuki Yoshikawa
Final approval of manuscript: Toshiharu Kamura, Ikuo Konishi, Hiroyuki Yoshikawa

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Clinical Trial Note

A Phase III Trial of Paclitaxel plus Carboplatin Versus Paclitaxel plus Cisplatin in Stage IVB, Persistent or Recurrent Cervical Cancer: Gynecologic Cancer Study Group/Japan Clinical Oncology Group Study (JCOG0505)

Isamu Saito[1], Ryo Kitagawa[2], Haruhiko Fukuda[1], Taro Shibata[1], Noriyuki Katsumata[3], Ikuo Konishi[4], Hiroyuki Yoshikawa[5] and Toshiharu Kamura[6]

[1]Clinical Trial and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, [2]Department of Gynecology and Obstetrics, Kanto Medical Center, NTT EC, [3]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, [4]Department of Obstetrics and Gynecology, Kyoto University, Kyoto, [5]Department of Obstetrics and Gynecology, Tsukuba University, Ibaraki and [6]Department of Obstetrics and Gynecology, Kurume University School of Medicine, Fukuoka, Japan

For reprints and all correspondence: Ryo Kitagawa, Department of Gynecology and Obstetrics, Kanto Medical Center, NTT EC, 5-9-22 Higashi-gotanda Shinagawa-ku, Tokyo 141-0022, Japan.
E-mail: kitagawa.ryo@east.ntt.co.jp

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A randomized controlled trial has been started in Japan to compare the utility of palliative chemotherapy containing paclitaxel and carboplatin (TC) with paclitaxel and cisplatin (TP) as a standard treatment for patients with the newly diagnosed Stage IVB, persistent or recurrent cervical cancer who are not amenable to curative treatment with local therapy. This trial was designed to evaluate the non-inferiority of TC as measured by the number of hospitalized days as an indicator of quality of life (QOL) when compared with TP combination therapy. The primary endpoint is overall survival. Secondary endpoints are progression-free survival, response rates, adverse events, severe adverse events and the proportion of non-hospitalization periods compared with planned treatment periods.

Key words: *cervical cancer – palliative chemotherapy – recurrent – persistent – Stage IVB – cisplatin – carboplatin – paclitaxel*

PROTOCOL DIGEST OF THE JCOG0505

Trial Backgrounds

The prognosis of patients with metastatic, recurrent or persistent cervical cancer who are not amenable to curative treatment with surgery and/or radiation therapy is still poor. Therefore, systemic chemotherapy is currently regarded as a key modality that should be further developed. The importance of combination chemotherapy as well as a single active or new agent is well recognized in the results of the Gynecologic Oncology Group (GOG) study. In a previous GOG study, single agent cisplatin was compared with cisplatin plus paclitaxel (TP) in patients with squamous cell cervical cancer. The combination therapy resulted in a higher response rate and longer median progression-free survival, but the overall survival between the two groups was similar (1). In another study that showed a survival benefit with multiagent therapy, single agent cisplatin was compared with cisplatin plus topotecan. However, this combination therapy had significantly higher toxicity (e.g. 70% versus 1.4% Grade 3 or 4 neutropenia) (2). A recent study reported promising results with TP combination therapy. In this study, incurable cervical cancer patients, including patients with adenocarcinoma or adenosquamous cell carcinoma, were randomly assigned to receive TP, cisplatin plus topotecan, or two other cisplatin-containing combinations. TP showed superiority over the other combination therapies in overall survival (3). Therefore, the present standard regimen in

Europe and the USA is TP combination therapy. However, we have also reported a promising and feasible combination chemotherapy consisting of paclitaxel and carboplatin (TC) in a Phase II study (4). Although as single agents, carboplatin has a lower response rate than cisplatin, the reduced nephrotoxicity of carboplatin does not require hydration, enabling a 3 h administration of paclitaxel in this combination therapy. Thus, TC combination has been available in the outpatient setting. Recently, non-squamous cell cervical cancer has been increasing and treating this disease is a significant priority. Our Phase II study targeted not only patients with squamous cell cervical cancer but also those with non-squamous cervical cancer. We have started a Phase III trial to evaluate the benefit and reduced toxicity of TC for incurable patients with either squamous or non-squamous cell cervical cancer.

The study protocol was designed by the Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG), approved by the Protocol Review Committee of the JCOG on 12 January 2006 and activated on 21 February 2006. This trial was registered at the UMIN Clinical Trials Registry as C000000335 (http://www.umin.ac.jp/ctr/index.htm).

Purpose

This prospective study aims to evaluate the clinical benefits of TC compared with TP for patients with Stage IVB, persistent or recurrent cervical cancer.

Study Setting

This study is a multi-institutional (30 specialized institutions), randomized controlled trial.

Resources

The study is supported in part by Health and Labour Science Research Grants for Clinical Research for Evidenced Based Medicine, Health and Labour Sciences Research Grant for Clinical Cancer Research, and Grants-in Aid for Clinical Cancer Research (17S-1, 17S-5, 20S-1 and 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint of the study is overall survival. Secondary endpoints are progression-free survival, response rates, adverse events, severe adverse events and the proportion of non-hospitalization periods compared with planned treatment periods. The last endpoint is intended to evaluate the reduced inconveniency of hospitalization with TC therapy as a surrogate for quality of life (QOL).

Eligibility Criteria

Inclusion Criteria

The inclusion criteria are as follows: (i) histologically proven uterine cervical cancer; (ii) squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the uterine cervix; (iii) one of the following: (a) newly diagnosed Stage IVB cervical cancer, (b) first relapse or persistent cervical cancer after curative or palliative first-line treatments, and (c) second relapse or persistent cervical cancer after curative or palliative second-line treatments including radiation therapy, chemotherapy, hormonal therapy or vaccination therapy; (iv) one of the following: (a) at least one metastatic lesion outside the pelvic cavity except in the paraaortic lymph node (LN) and/or inguinal LN, (b) no metastatic lesions outside the pelvic cavity except in the paraaortic LN and/or inguinal LN, and at least one of these lesions has been irradiated, and (c) all lesions are localized inside the pelvic cavity, and at least one of them has been irradiated; (v) recovery from effects of any prior therapy (at least 2 weeks from the last surgery or the last administration of chemotherapy alone, 3 weeks from radiotherapy alone and 4 weeks from the last administration of concurrent chemoradiotherapy); (vi) no previous treatment with >51 Gy of palliative radiation therapy; (vii) no prior surgical resection of pulmonary metastases or radical resection of recurrent lesions inside the pelvic cavity including pelvic exenteration; (viii) no bilateral hydronephrosis; (ix) no prior chemotherapy, or only one platinum-containing regimen; (x) no prior chemotherapy including taxanes; (xi) age ≥ 20 and ≤ 75 years; (xii) an Eastern Cooperative Oncology Group performance status (PS) of 0–2; (xiii) sufficient marrow, liver, kidney function and normal ECG; and (xiv) written informed consent.

Exclusion Criteria

The exclusion criteria are as follows: (i) neurological disturbance with functional disorder; (ii) symptomatic central nervous system metastasis; (iii) hypersensitivity to alcohol; (iv) active bacterial infection; (v) hepatitis B surface antigen-positive; (vi) poorly controlled hypertension; (vii) history of myocardiac infarction within 6 months; (viii) unstable angina; (ix) poorly controlled diabetes; (x) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*; (xi) pregnant or lactating; (xii) mental disease or mental symptoms that would affect the participant's decision to participate; and (xiii) continuous systemic steroid therapy.

Treatment Methods

Chemotherapy is administered as follows. The TP regimen (standard arm) is paclitaxel 135 mg/m^2 intravenously (IV) for 24 h on day 1, followed by cisplatin 50 mg/m^2 IV for 2 h on day 2, which is repeated every 21 days. The TC regimen

(experimental arm) is paclitaxel 175 mg/m^2 IV for 3 h on day 1, followed by carboplatin at an area under the curve of 5 IV for 1 h on day 1, which is repeated every 21 days. The premedication for paclitaxel with steroids, H1 blocker and H2 blocker is mandatory in both arms. Both regimens are administered for a maximum of six cycles for both responders and non-responders, or until disease progression or unacceptable toxicity prohibited additional therapy.

The Common Terminology Criteria for Adverse Events (CTCAE v3.0) is used for dose modifications. All patients are required to have absolute neutrophil counts $>1500/mm^3$, platelet counts $>75\,000/mm^3$ and acceptable levels of some non-hematologic toxicities <3 days before the treatment course or treatment is delayed until blood counts and non-hematologic toxicities return to acceptable levels. At the time of re-treatment, chemotherapy doses are adjusted based on nadir blood counts and interval toxicity. If necessary, patients are permitted to receive filgrastim.

A response was defined according to the RECIST criteria and generally evaluated after three courses and/or the last course of therapy.

Follow-up

All patients are followed up for 1 year after the study is closed for entry. Neurological adverse events are checked every 4 weeks, and the efficacy assessments are evaluated every 2 or 3 months.

Study Design and Statistical Methods

This study was designed as a randomized Phase III trial to demonstrate the non-inferiority of TC compared with standard TP using overall survival as the primary endpoint. Patients are randomized to each treatment arm by a minimization method with institution, PS (0, 1 or 2), histology (squamous cell carcinoma or adenocarcinoma) and tumor sites (all of them had prior radiotherapy or chemoradiotherapy or no therapy) as balancing factors at the JCOG Data Center (5,6). If TC is not inferior to TP in terms of overall survival and is comprehensively superior in terms of other secondary endpoints of safety or QOL, TC will be the preferred treatment. The corresponding null hypothesis is that the hazard ratio of TC to TP is >1.29, the non-inferiority margin. It corresponds that the mean survival time (MST) of TC is inferior to TP (9 months) by >2 months under the proportional hazard assumption. Assuming exponential distributions and that the MST of TC is 10 months, 234 patients are needed to have $>80\%$ power to confirm the non-inferiority with one-sided α 5% after a 1-year follow-up period with 2.5 years of accrual. Even if MST of TC is 9.5 months, at least 70% of power is attained by 242 patients. On the basis of these considerations, the planned sample size is 250.

The primary endpoint is to be analyzed based on the Cox proportional hazard model with PS and histology as stratified factors. If the upper limit of the 90% confidence interval of the hazard ratio is <1.29, the non-inferiority of TC to TP in terms of overall survival is confirmed. This study started in February 2006 with a planned accrual period of 2.5 years. The accrual of it, however, had been slow and the accrual period was revised to 3.5 years.

Interim Analysis and Monitoring

Interim analysis is scheduled once when half of the planned sample size has been accumulated and just after the nearest periodical monitoring data are available. Multiplicity is adjusted by the Lan and DeMets method with O'Brien and Fleming type boundaries. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis report and determine whether the study should be stopped early. In-house interim monitoring will be performed by the JCOG Data Center to ensure data submission and study progress. The monitoring reports will be submitted to and reviewed by the GCSG every 6 months.

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Hokkaido University Hospital, Sapporo Medical University, Tohoku University Hospital, Institute of Clinical Medicine, Tsukuba University Hospital, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center (Saitama Medical School), Jikei Kashiwa Hospital, National Cancer Center Hospital, Jikei University Hospital, Cancer Institute Hospital, The University of Tokyo Hospital, Juntendo University School of Medicine, Kitasato University School of Medicine, Niigata Cancer Center Hospital, Sinshu University, Aichi Cancer Center Hospital, Osaka City University Medical School, Kinki University School of Medicine, Kyoto University Hospital, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City General Hospital, Sakai Hospital, Kinki University School of Medicine, Hyogo Cancer Center Hospital, Faculty of Medicine, Tottori University, National Hospital Organization Kure Medical Center Chugoku Cancer Center, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center, Kurume University School of Medicine, Kyushu University Hospital, Faculty of Medicine, Saga University and Kagoshima City Hospital.

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Conflict of interest statement

None declared.

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A Randomized Phase II/III Trial of 3 Weekly Intraperitoneal versus Intravenous Carboplatin in Combination with Intravenous Weekly Dose-dense Paclitaxel for Newly Diagnosed Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Keiichi Fujiwara[1,*], Eriko Aotani[2], Tetsutaro Hamano[2], Shoji Nagao[1], Hiroyuki Yoshikawa[3], Toru Sugiyama[4], Junzo Kigawa[5], Daisuke Aoki[6], Noriyuki Katsumata[7], Masahiro Takeuchi[2] and Mitsuaki Suzuki[8]

[1]Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka-City, Saitama, [2]Clinical Trial Coordinating Center, Kitasato University Research Center for Clinical Pharmacology, Tokyo, [3]Department of Obstetrics and Gynecology, Tsukuba University, Tsukuba, Ibaraki, [4]Department of Obstetrics and Gynecology, Iwate Medical University, Iwate, [5]Department of Gynecologic Oncology, Tottori University Cancer Center, Yonago, Tottori, [6]Department of Obstetrics and Gynecology, Keio University, Shinjuku-ku, [7]Division of Medical Oncology, National Cancer Center Hospital, Tokyo and [8]Department of Obstetrics and Gynecology, Jichi Medical University, Shimono, Tochigi, Japan

*For reprints and all correspondence: Keiichi Fujiwara, Department of Gynecologic Oncology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka-City, Saitama 350-1298, Japan. E-mail: fujiwara@saitama-med.ac.jp

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Retrospective studies and a Phase II trial demonstrated the promising efficacy and safety of intraperitoneal administration of carboplatin in ovarian, fallopian tube and primary peritoneal cancer. A Japanese Gynecologic Oncology Group 3016 randomized Phase III trial for these cancers showed dose-dense weekly administration of paclitaxel significant improvement of progression-free survival and overall survival over every 3-week administration. From June 2010, we have been conducting a randomized Phase II/III trial of intravenous versus intraperitoneal administration of carboplatin every 3 week in combination with dose-dense weekly administration of paclitaxel. The purpose of this trial is to prove the superiority of intraperitoneal administration of carboplatin over intravenous administration. Primary endpoint is progression-free survival and secondary endpoints include overall survival, quality of life assessment and cost–benefit. The first 120 patients will be evaluated for the feasibility of intraperitoneal arm and a total of 746 patients will be enrolled in a Phase III study.

Key words: ovarian cancer – intraperitoneal chemotherapy – carboplatin – paclitaxel – dose-dense chemotherapy

INTRODUCTION

In Japan, it is estimated that incidence of epithelial ovarian cancer is approximately 8000 per year and almost half of the patients died of this disease. There is no established screening method; therefore, 60–70% of the patients are at Stages III or IV when newly diagnosed. A standard treatment strategy for the advanced ovarian cancer is a maximum debulking surgery followed by chemotherapy. The standard chemotherapy regimen has been a combination of carboplatin at AUC of 5–6 and paclitaxel at 175 mg/m^2 given intravenously every 3 weeks (1). This regimen has been utilized as standard since 1999, yet the prognosis of advanced ovarian cancer is poor. Numerous efforts have been made to improve the survival, and two distinct innovations on the chemotherapy were achieved recently, which are intraperitoneal chemotherapy and weekly dose-dense administration of paclitaxel.

Three large randomized trials have been conducted in the USA and all of them showed improvement of overall survival (OS) and/or progression-free survival (PFS) (2–4). US National Cancer Institute and Gynecology Oncology Group (GOG) conducted a metanalysis and found that

intraperitoneal (IP) chemotherapy improved OS at the hazard ratio of 0.78 (5). In response to this result, US NCI has issued a clinical announcement in 2006 to recommend IP cisplatin-based chemotherapy for optimally debulked Stage III ovarian cancer patients. In spite of these efforts, IP chemotherapy has not been accepted in the gynecologic cancer community, mainly because of the toxicity. It is expected that replacement of cisplatin to carboplatin may reduce the toxicity without sacrificing the efficacy (6).

Another innovation was the application of dose-dense weekly paclitaxel. Japanese Gynecologic Oncology Group (JGOG) has conducted a large-scale randomized trial and demonstrated significant improvement in PFS and OS (7).

Therefore, it is of great expectation that the combination of dose-dense weekly administration of paclitaxel with IP administration of carboplatin will improve the prognosis further.

This protocol was designed by the Protocol Committee of Gynecologic Oncology Trial and Investigation Consortium (GOTIC) and Ovarian Committee member of JGOG. The protocol was approved by Clinical Trial Review Committee of GOTIC as GOTIC-001 on 9 September 2009, and that of JGOG as JGOG-3019 on 26 April 2010. The protocol was submitted for the Evaluation System of Investigational Medical Care of Ministry of Health, Labor and Welfare, Japan, and was approved to conduct under the Japanese governmental health insurance system on 16 April 2010. This trial was registered at the UMIN Clinical Trials Registry as UMIN000003670 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF GOTIC-001/JGOG-3019

Purpose

This study was designed to prove superiority of IP administration of carboplatin over IV administration in newly diagnosed carcinoma of the ovary, fallopian tube and primary peritoneum. The combination of paclitaxel is the dose-dense weekly fashion based on the JGOG-3016 trial result.

Study Setting

This is a multi-institutional randomized Phase II/III trial.

Resource

Grants-in Aid for Cancer Research (H21−014), from the Ministry of Health, Labor and Welfare, Japan. Gynecologic Oncology Trial and Investigation Consortium and JGOG support this trial.

Endpoints

The primary endpoint of this study is PFS. Secondary endpoints are OS, response rate in patients with measurable disease, quality of life assessment and cost–benefit.

Eligibility Criteria

(i) The patient must be planned to undergo laparotomy surgery for formal registration. Since this trial includes patents with both optimal and suboptimal residual disease, the patients with exploratory laparotomy are also eligible.
(ii) Patient who is preoperatively anticipated to be FIGO II to IV epithelial ovarian, fallopian tube or primary peritoneal cancer is eligible for pre-registration. And the patient must be clinically at Stages II–IV at the time of formal registration.
(iii) Patient who signed the consent for the placement of IP port system when she is assigned to the IP arm.
(iv) The patients who are planned to receive chemotherapy within 8 weeks after initial surgery.
(v) ECOG performance status must be 0–2.
(vi) Patient must have adequate organ functions.
(vii) Survival can be expected 3 month or more.
(viii) Age 20 or older.

Written informed consent must be obtained from the patient or legal guardian.

Exclusion Criteria

(i) Patients with borderline malignancies.
(ii) Patients who have received chemotherapy or radiation therapy for the current disease before enrolment.
(iii) Patients with any of the active concurrent malignancies or past history of malignancies of which the follow-up is within 5 years.
(iv) Patients with severe complications: patients with severe heart disease or cerebrovascular disease, or uncontrolled diabetes or hypertension, pulmonary fibrosis, interstitial pneumonitis, active bleeding, active gastrointestinal ulcer or sever neuropathy.
(v) Patients with history of hypersensitivity polyoxyethylene castor oil.
(vi) Patients with pleural effusion that need continuous drainage.
(vii) Patients with active infectious disease.
(viii) Patients with possibility of pregnancy or under breast-feeding.
(ix) Patients with symptomatic brain metastasis.
(x) Patients whose circumstances at the time of entry onto the study would not permit completion of study or required follow-up.

Study Flow

The patient who is anticipated to have Stage II, III or IV carcinoma of the ovary, fallopian tube or primary peritoneum will be pre-registered through Web Registration System of Kitasato University Clinical Trial Coordinating Center (CTCC), after written informed consent was obtained. At the time of surgery, the physician will call to the Kitasato CTCC

before closure of the abdominal wall. The coordinator will ask the stratification factors, clinical stages and the size of residual disease, then randomization result will be informed. This is considered as a formal registration. When the patient is randomized to IP arm, the Bard IP Port (#14 Fr) will be placed according to the surgical manual. For patient who randomized to the IV arm, IP port will not be placed. The protocol chemotherapy will be started within 8 weeks after confirmation of histology as epithelial cancer.

Control Arm Treatment

For patients randomized to IV arm will receive paclitaxel at 80 mg/m^2 as 1 h intravenous (IV) infusion followed by carboplatin at AUC 6 as a 30–120 min IV infusion on Day 1. IV administration of paclitaxel will be repeated at 80 mg/m^2 on days 8 and 15. This regimen is considered as one cycle.

Experimental Arm Treatment

For patients randomized to IP arm will receive paclitaxel at 80 mg/m^2 as 1 h IV infusion. During the paclitaxel infusion, 1000–1500 ml physiological saline or 5% glucose will be administered through IP port. This will allow the confirmation that IP port is not obstructed and dense adhesion does not occur surrounding the catheter. After completion of the hydroperitoneum, carboplatin at AUC 6 will be infused. To confirm that the hypersensitivity of carboplatin does not occur, 10 ml will be administered and after waiting for 10 min, the rest of the amount will be infused. These procedures will be done on day 1. IV administration of paclitaxel will be repeated at 80 mg/m^2 on days 8 and 15. This regimen is considered as one cycle.

Number of Cycles

The protocol treatment will be repeated for six cycles for patients with chemotherapy only after primary surgery. However, in patient, who will undergo interval debulking surgery after response to the suboptimal residual disease, they may receive up to eight cycles. Interval debulking surgery can be performed after three to five cycles of protocol chemotherapy, and then patient can receive three more cycles of chemotherapy.

Study Design and Statistical Considerations

This study was designed as a randomized Phase II/III trial. Target sample sizes and event were as follows.

Phase A: 60 patients/arm
Phase B: 510 events (target sample size: 746 patients, including Phase A patients)

Planned patient accrual duration is 3 year and planned follow-up duration will be either 3 year or until the time when the 510 events are observed, whichever it comes first.

Sample sizes were determined based on the following considerations.

Phase II Part (Phase A)

In the previous JGOG-3016 study, treatment completion rate for dose-dense pacliaxel plus carboplatin (dd-TC) was 47.0%, and hematologic adverse event (more than or equal to grade 3) rate for dd-TC was the following, neutropenia: 91.7%, leukocytes: 80.4%, hemoglobin: 68.6%, platelets: 43.6%. Furthermore, the response rate for dd-TC was 55.8%. According to above evidence, we performed statistical simulations for these factors to find a sample size which would be necessary to obtain 95% confidence intervals of these estimates with 15% precisions in the IV arm, and we calculated that 46 patients is needed. We also assumed that treatment completion rate in the IP arm is expected to be lower than the IV arm and hematologic adverse event rates defined above are expected to be higher, thereby the required sample size in the IP arm would be larger than those of the IV arm. Furthermore, we also assumed that some patients would not have a measurable site. Thus, we plan the sample size of 120 patients (60 patients for each arm) to be targeted. Phase II patients will be included in the Phase III analysis.

Phase III Part (Phase A + Phase B)

The primary endpoint of this study is PFS. In the previous JGOG3016 study, the median PFS was approximately 28 months for dd-TC. Furthermore, in a meta-analysis conducted by the National Cancer Institute (NCI) and the Gynecologic Oncology Group, the hazard ratio for PFS in the IP as compared with the IV was 0.784, indicating the 21.6% hazard reduction in the IP treatment).

According to above evidence, we assumed that the median PFS was 28 months for the IV arm and the hazard ratio for PFS in the IP arm as compared with the IV arm was 0.78. The 22% hazard reduction would be acceptable as a new standard treatment regimen. With an accrual period of 3 years and a minimum follow-up period of 3 years, 746 patients (373 patients for each arm) and 510 events (239 in IP arm) are required in order to detect this hazard ratio using the log-rank test with an overall two-sided type I error of 0.05 and a power of 80%. The final analysis will be performed either after the required events will be observed or after the minimum follow-up period will be completed, whichever comes first. If the required events will not be observed after the minimum follow-up period will be completed, extension of the follow-up duration will be considered.

Randomization and Stratifications

Patients will be centrally randomized. A minimization technique will be used for random treatment allocation stratifying by the enrolling institutions, initial FIGO stage of disease (II, III or IV) and the size of residual disease (complete, less than 1 cm, between 1 and 2 cm and more than 2 cm).

Analysis Method

Phase III part: analysis set. Efficacy analyses will be performed on all randomly assigned patients based on the intent-to-treat principle. Patients receiving at least one partial infusion of the study drug will be qualified for safety analysis.

Primary efficacy analysis. The PFS curves will be estimated using Kaplan–Meier method. Non-parametric 95% confidence intervals will be calculated for the median PFS, and the curves will be compared in the two treatment groups based on the two-sided log-rank test with an overall significance level of 5%. Multiplicity adjustments in regard to interim analysis will be noted in the section of the interim analysis.

Secondary efficacy analysis. The OS curves will be also estimated using Kaplan–Meier technique and compared using log-rank test. The response rates in the case with measurable site, and the treatment completion rates will be estimated by arms. We define the treatment completion case as the patient who receives treatment to the sixth cycle. Exact 95% confidence intervals will be calculated for each response rate and treatment completion rate. The rates for the two treatment groups will be compared using Fisher's exact test and a normally approximated 95% confidence interval for the odds ratio.

Interim analysis. Under the proportional hazard assumption, alternative hypothesis and uniformly patients' enrollment, the half of the required events (255 events) would be observed when approximately 3.2 years go by from a starting point of this trial. One interim analysis will be carried out either when 3.5 years go by from a starting point of this trial or when the required events will be observed, whichever comes first. In order to maintain an overall significance level of 5%, the PFS curves would be compared with Type I error of 0.3% in the interim analysis and of 4.7% in the final analysis calculated by the O'Brien and Fleming-type alpha spending function.

Subgroup analysis. In order to support analyses of primary and secondary endpoints, all comparisons and estimates will be stratified by randomization factors and other demographic data.

Exploratory analysis. Statistical models (e.g. Cox's proportional hazard model and logistic regression model) will be used for further explorations.

Safety analysis. The number of patients for each adverse event will be summarized for each treatment group. The rates of adverse events will be estimated for each group and compared using an approximate 95% confidence interval for the odds ratio.

Quality of life and Cost-effectiveness analyses. Quality of life (QOL) and cost-effectiveness (CE) of IP arm and IV arm will be analyzed when 2 years go by from a starting point of this trial, assuming that 300 qualified patients would be observed at that time. CE data are also analyzed at the same time of QOL analysis. These endpoints will also be analyzed after the study completion (or study termination) with efficacy endpoints. Baseline QOL score will be analyzed using linear model adjusting for age and baseline ECOG performance status (PS). Other QOL scores will be analyzed using linear mixed model with age, PS and baseline QOL scores. Further details of QOL and CE analysis will be specified in the statistical analysis plan.

Analysis results of QOL evaluation will be published after 2 years go by from a starting point of this trial, assuming that 300 qualified patients would be observed at that time. For CE analysis, we define the analysis set of all patients who will be registered and agreed with informed consents of CE analysis. Analysis and report of cost-effectiveness with primary endpoints will be reviewed.

Feasibility Analysis. In the Phase II period, the feasibility of combination of IV dose-dense paclitaxel and IP carboplatin will be evaluated. The number of patients for treatment completion, hematologic and non-hematologic toxic effects will be summarized for each treatment group. The rates of toxic effects will be estimated for each group. Furthermore, the rates at the end of the treatment will be estimated for each treatment group. Exact 95% confidence intervals will be calculated for each rate. These rates for the two treatment groups will be compared using Fisher's exact test and an approximate 95% confidence interval for the odds ratio to aid the IDMC in reaching decisions about study continuation.

Study Monitoring

Study monitoring will be performed by the Kitasato University Clinical Trial Coordinating Center, to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. On-site monitoring on the selective institution will be performed once a year. The monitoring reports will be submitted to the Independent Data and Safety Monitoring Committee every 6 months.

Participating Institutions

Leading institution as the study under the Evaluation System of Investigational Medical Care (ESIMeC) is Saitama Medical University International Medical Center. Other institutions waiting for the governmental approval for the ESIMeC as of 15 July 2010 are as follows. Iwate University, Jichi Medical University, Keio University, National Cancer Center Hospital, Tottori University, Tsukuba University, Gunma University and Saitama Medical University Medical Center. Other institutions are under the process of ESIMeC submission.

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Conflict of interest statement

None declared.

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Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin

Toshiaki Takahashi,[1,7] Eishin Hoshi,[2] Masakazu Takagi,[3] Noriyuki Katsumata,[4] Masaaki Kawahara[5] and Kenji Eguchi[6]

[1]Thoracic Oncology Division, Shizuoka Cancer Center, Sunto-gun, Shizuoka; [2]Department of Thoracic Surgery, Saitama Cardiovascular and Respiratory Center, Saitama; [3]Department of Surgery, Shizuoka General Hospital, Shizuoka; [4]Department of Medical Oncology, National Cancer Center Hospital, Tokyo; [5]Department of Respiratory Medicine and Medical Oncology, Otemae Hospital, Osaka; [6]Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan

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Aprepitant is a new neurokinin-1 (NK_1) receptor antagonist developed as a treatment for chemotherapy-induced nausea and vomiting (CINV). To evaluate the efficacy and safety of aprepitant used in combination with standard therapy (granisetron and dexamethasone), we conducted a multicenter, phase II, placebo-controlled, double-blind, randomized study in Japanese cancer patients who received cancer chemotherapy including cisplatin (≥70 mg/m^2). Aprepitant was administered for 5 days. A total of 453 patients were enrolled. In the three study groups, (i) standard therapy, (ii) aprepitant 40/25 mg (40 mg on day 1 and 25 mg on days 2–5) and (iii) aprepitant 125/80 mg (125 mg on day 1 and 80 mg on days 2–5), the percentage of patients with complete response (no emesis and no rescue therapy) was 50.3% (75/149 subjects), 66.4% (95/143 subjects) and 70.5% (103/146 subjects), respectively. This shows that efficacy was significantly higher in the aprepitant 40/25 mg and 125/80 mg groups than in the standard therapy group (χ^2 test [closed testing procedure]: $P = 0.0053$ and $P = 0.0004$, respectively) and highest in the aprepitant 125/80 mg group. The delayed phase efficacy (days 2–5) was similar to the overall phase efficacy (days 1–5), indicating that aprepitant is effective in the delayed phase when standard therapy is not very effective. In terms of safety, aprepitant was generally well tolerated in Japanese cancer patients. (ClinicalTrials.gov number, NCT00212602.) (*Cancer Sci* 2010; 101: 2455–2461)

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse event observed in more than 90% of patients treated with highly emetogenic antitumor agents, especially cisplatin.[1,2]

In general, CINV persists for approximately 5 days.[3] The CINV that occurs within 24 h after administration of antitumor agents is defined as acute phase CINV, and delayed phase CINV occurs 2–5 days after administration of antitumor agents. It has been reported that the incidence of nausea/vomiting induced by cisplatin, the most highly emetogenic antitumor agent, is 98% in the acute phase and 77% in the delayed phase after administration of 50 mg/m^2 or higher doses without preventive treatment.[4]

As of October 2009 in Japan, the standard antiemetic therapy for CINV is a 5-HT_3 receptor antagonist plus dexamethasone. In the presence of this therapy, CINV is known to occur in approximately 25 and 50% of patients treated with highly emetogenic antitumor agents in the acute and delayed phases, respectively.[5] In addition, the percentage of patients who developed CINV under standard antiemetic therapy increased from approximately 50% in the first course of cancer chemotherapy to approximately 75% in the sixth course.[6,7] In several clinical studies of a 5-HT_3 receptor antagonist with dexamethasone, no efficacy was demonstrated for CINV in the delayed phase.[3,8]

Aprepitant is a neurokinin-1 (NK_1) receptor antagonist developed as a treatment for CINV. It acts by inhibiting the binding of substance P to the NK_1 receptor in the vomiting center, and when used with standard antiemetic therapy (5-HT_3 receptor antagonist and dexamethasone) it has been shown to be effective for CINV (especially for delayed CINV) induced by highly and moderately emetogenic cancer chemotherapy.[9–12] Overseas guidelines recommend the use of aprepitant in combination with a 5-HT_3 receptor antagonist and dexamethasone to prevent nausea/vomiting induced by highly and moderately emetogenic cancer chemotherapy.[13–15] While the efficacy and safety of aprepitant has been established in other countries, no study has been conducted in Japanese patients.

Therefore, we conducted a multicenter, placebo-controlled, double-blind, randomized, parallel comparative study to evaluate the efficacy and safety of aprepitant plus standard therapy (granisetron and dexamethasone) to prevent CINV in Japanese cancer patients undergoing treatment with chemotherapy including a highly emetogenic cisplatin-based regimen (≥70 mg/m^2).

Materials and Methods

Patient selection. Japanese cancer patients aged 20 years and older who received cancer chemotherapy including cisplatin at a dose of ≥70 mg/m^2 were included in the present study. If at least moderately (Hesketh level ≥3) emetogenic antitumor agent other than cisplatin was concomitantly used, it had to be administered on the same day with cisplatin (day 1). With a Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0–2 and an estimated life expectancy of at least 3 months, patients had to meet the following laboratory criteria: white blood cell count ≥3000/mm^3; neutrophil count ≥1500/mm^3; platelet count ≥100 000/mm^3; aspartate aminotransferase (AST) (glutamic oxaloacetic transaminase (GOT)) and alanine aminotransferase (ALT) (glutamic pyruvic transaminase (GPT)) ≤2.5 × upper limit of the normal range at the facility; total bilirubin ≤1.5 × upper limit of the normal range at the facility; and creatinine ≤1.5 × upper limit of the normal range at the facility. The following patients were excluded from the study: patients with a risk of vomiting for other reasons (symptomatic brain metastasis, meningeal infiltration, epilepsy, active peptic ulcer, gastrointestinal obstruction, concomitant abdominal, pelvic radiotherapy, etc.); and pregnant, nursing or possibly pregnant women. After the protocol and informed consent form were

[7]To whom correspondence should be addressed. E-mail: t.takahashi@scchr.jp

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approved by the Institutional Review Board (IRB) at each facility, patients who gave written informed consent were enrolled.

Study design. This was a multicenter, placebo-controlled, double-blind, randomized, parallel comparative study and conducted in a total of 127 institutions in Japan. Patients who met all of the inclusion criteria and none of the exclusion criteria were allocated to the aprepitant 125/80 mg group (oral administration at a dose of 125 mg on day 1 and a dose of 80 mg on days 2–5), aprepitant 40/25 mg group (oral administration at a dose of 40 mg on day 1 and a dose of 25 mg on days 2–5) or the standard therapy group (oral administration of placebo on days 1–5). Treatment assignment (dynamic allocation) was performed using a minimization method for balancing four factors (sex, presence or absence of at least one emetogenic antitumor agent used in combination with cisplatin, presence or absence of previous treatment with cisplatin, and institution) between the treatment and control groups. All patients received standard therapy consisting of intravenous granisetron (40 μg/kg on day 1) and dexamethasone. The dose of each drug in each group is shown in Table 1. Because it is a substrate and inhibitor of CYP3A4, aprepitant is known to increase the plasma dexamethasone concentration.[9] Therefore, to achieve comparable plasma levels of dexamethasone in the presence and absence of aprepitant in this study, the dose of dexamethasone was 6 mg on day 1 and 4 mg on days 2 and 3 in the 125/80 mg group (50% of the dose in the absence of aprepitant), and 8 mg on day 1 and 6 mg on days 2 and 3 in the 40/25 mg group (75% of the dose in the absence of aprepitant).

On day 1, administration of the first at least moderately (Hesketh level ≥3) emetogenic antitumor agent (including cisplatin) was started 1.5 h after oral administration of aprepitant or placebo and 30 min after intravenous administration of granisetron and dexamethasone (over 30 min or less). On day 2 and thereafter, aprepitant or placebo was orally administered in the morning, followed by intravenous administration of dexamethasone 1 h later.

Concomitant use of other antiemetics was prohibited from 48 h before day 1 to the morning of day 6, except for rescue therapy for CINV.

Assessments. Patients recorded the onset of vomiting and nausea in a symptom diary from day 1 to the morning of day 6. Vomiting was defined as at least one episode of emesis or gagging and was distinguished from other episodes if emesis was not observed for at least 1 min. For nausea, patients recorded the most severe intensity during the previous 24-h period based on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). After rescue therapy was administered (defined as a drug prescribed by a physician to reduce nausea/vomiting), the date/time, name of the drug, dose and reason for use were recorded. Efficacy was evaluated from the start of administration of the first at least moderately emetogenic antitumor agent (including cisplatin) on day 1 (also defined as 0 h) to the morning on day 6 (120 h).

Table 1. Dose of each drug in each group

Treatment group	Drug	Day 1	Days 2–3	Days 4–5
Aprepitant 125/80 mg regimen	Aprepitant (po)	125 mg	80 mg	80 mg
	Dexamethasone (i.v.)	6 mg	4 mg	–
	Granisetron (i.v.)	40 μg/kg	–	–
Aprepitant 40/25 mg regimen	Aprepitant (po)	40 mg	25 mg	25 mg
	Dexamethasone (i.v.)	8 mg	6 mg	–
	Granisetron (i.v.)	40 μg/kg	–	–
Standard therapy	Aprepitant (po)	Placebo	Placebo	Placebo
	Dexamethasone (i.v.)	12 mg	8 mg	–
	Granisetron (i.v.)	40 μg/kg	–	–

i.v., intravenous; po, per os.

Safety was evaluated on the basis of physical examination findings (which included vital signs, bodyweight, general laboratory tests and electrocardiogram) and adverse events (clinical findings and laboratory values recorded until day 15). Toxicity grades were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0.

Statistical analysis. Based on the results of combined analysis from overseas phase III studies (studies 052 and 054)[16] that the percentage of patients with complete response in the overall phase was 67.7% in the 125/80 mg group and 47.8% in the placebo group, a sample size of 115 subjects per group was estimated to be required to provide a power of approximately 80%. On the assumption that approximately 15–20% of subjects would be withdrawn or drop out, a target sample size of 130–140 subjects per group (390–420 subjects in total) was selected. The analysis for efficacy was performed on the full analysis set (FAS) data. The FAS population was the set of all randomized subjects after minimal and justified elimination, who were treated with granisetron hydrochloride and dexamethasone phosphate (at least one dose), who kept a symptom diary, and who received at least one dose of the study drug. The primary efficacy end-point was the percentage of patients with complete response (defined as no emetic episode and no rescue therapy). The secondary efficacy end-points were the percentage of patients with: (i) no emesis; (ii) no rescue therapy; (iii) complete protection (no emesis, no rescue therapy and no significant nausea [nausea score: 0 and 1]); (iv) total control (no emesis, no rescue therapy and no nausea [nausea score: 0]); (v) no significant nausea (nausea score: 0 and 1); and (vi) no nausea (nausea score: 0). Both the primary and secondary end-points were assessed in the overall phase (days 1–5), acute phase (day 1) and delayed phase (days 2–5). The χ^2 test was performed at a two-tailed significance level of 0.05 to compare the efficacy between standard therapy and the 125/80 mg groups, and between standard therapy and the 40/25 mg groups. For a complete response in the overall phase, a closed testing procedure was used to control the overall Type I error at 0.05 beginning with the 125/80 mg group and then the 40/25 mg group.

The population used for analysis of the safety data included subjects with the target disease who received at least one dose of the study drug. The incidence of adverse events and adverse drug reactions (adverse events for which a causal relationship could not be ruled out) was calculated in each group and compared between groups using the χ^2 test at a two-tailed significance level of 0.05.

Results

Patients. A total of 453 patients were enrolled in the present study and allocated to one of three groups (151 patients per group) (Fig. 1). Of these, 449 patients were included in the safety analysis set, 439 subjects were included in the FAS. Table 2 shows their demographic characteristics. All baseline factors were similar across the groups, including age, sex, height, bodyweight and cisplatin dose, as well as known risk factors for CINV (female, motion sickness, history of CINV, etc.).

Efficacy. The primary end-point was the percentage of patients with complete response (no emesis and no rescue therapy) over the entire treatment course, and the results for each treatment are shown in Figure 2. Efficacy of aprepitant was significantly higher than efficacy of standard therapy (125/80 mg group, 70.5% [103/146]; 40/25 mg group, 66.4% [95/143]; standard therapy group, 50.3% [75/149]; 125/80 mg group *versus* standard therapy group, $P < 0.001$; 40/25 mg group *versus* standard therapy group, $P < 0.01$). The acute- and delayed-phase efficacies are shown in Figure 3. While the delayed phase

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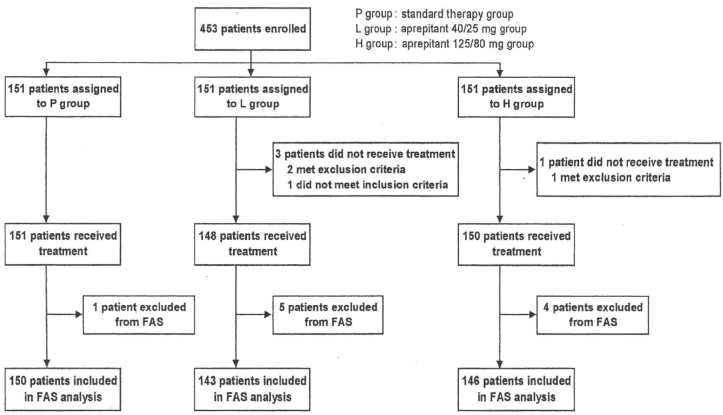

Fig. 1. Study flow chart. FAS, full analysis set.

efficacy (125/80 mg group, 72.6% [106/146]; 40/25 mg group, 69.9% [100/143]; standard therapy group, 51.7% [77/149]; 125/80 mg group *versus* standard therapy group, $P < 0.001$; 40/25 mg group *versus* standard therapy group, $P < 0.01$) was similar to the overall phase efficacy, the percentage of patients with a complete response was higher (but not significantly higher) in both aprepitant groups than in the standard therapy group in the acute phase (125/80 mg group, 87.0% [127/146]; 40/25 mg group, 90.2% [129/143]; standard therapy group, 83.3% [125/150]). In addition, subgroup analysis of patients with a complete response in the overall phase performed after stratification for sex, age and previous treatment with cisplatin showed that the overall phase efficacy of aprepitant was consistently higher than that of standard therapy, irrespective of these factors (Table 3).

For each secondary end-point and each treatment, the overall phase, acute phase and delayed phase efficacies are shown in Table 4. In the overall phase, the percentage of patients with "no emesis" was significantly higher in the 125/80 mg and 40/25 mg groups than in the standard therapy group ($P < 0.001$ for both). The percentage of patients with "complete protection" and "no significant nausea" was significantly higher in the 125/80 mg group than in the standard therapy group ($P < 0.01$ and $P < 0.05$, respectively), but was not significantly different between the 40/25 mg and standard therapy groups. The percentage of patients with "total control," "no rescue therapy" or "no nausea" was numerically higher in the 125/80 mg and 40/25 mg groups, but not significantly different from the standard therapy group. In the acute phase, secondary end-points were not significantly different between the aprepitant groups and the standard therapy group. In the delayed phase, on the other hand, the percentage of patients with "no emesis" was significantly higher in the 125/80 mg and 40/25 mg groups than in the standard therapy group ($P < 0.0001$ for both), whereas the percentage of patients with "complete protection" and "no significant nausea" was significantly higher in the 125/80 mg group than in the standard therapy group ($P < 0.01$ for both), but was not significantly different between the 40/25 mg and standard therapy groups.

Tolerability. All 453 enrolled subjects were included in the safety analysis. Adverse events that occurred within 15 days after the start of treatment with the study drug are summarized in Table 5. In all groups, the incidence of adverse events was high and not different across the groups. The incidence of drug-related adverse events was also not significantly different between each of the aprepitant groups and the standard therapy group. In addition, the distribution of toxicity grades (NCI-CTCAE grades indicating severity of adverse events or drug-related adverse events) was not markedly different across the groups. In terms of clinical findings, the most common adverse event was anorexia. Other adverse events (clinical findings) with an incidence of ≥10% in any group were constipation, hiccups, malaise, diarrhea, nausea, vomiting, pyrexia and insomnia. In terms of laboratory values, the incidence of common adverse events (including decreased white blood cell count, neutrophil count, platelet count, lymphocyte count and decreased hemoglobin) were similar across the groups. The incidence of the most common drug-related adverse events (hiccups) was similar across the groups (125/80 mg group, 10.0%; 40/25 mg group, 6.1%; standard therapy group, 9.3%). The incidence of febrile neutropenia as well as that of other infection-related adverse events was not different across the groups. Since interactions between aprepitant (which has an inhibitory effect on CYP3A4) and antitumor agents metabolized by CYP3A4 are possible, the correlation of the incidence of adverse events and drug-related adverse events with the concomitant use of antitumor agents metabolized by CYP3A4 (cyclophosphamide, etoposide, vincristine sulfate, vinblastine sulfate, vindesine sulfate, irinotecan hydrochloride, docetaxel hydrate, vinorelbine ditartrate, ifosfamide and gefitinib) was examined. Antitumor agents metabolized by CYP3A4 were used in 103 (68.7%) of 150 patients in the 125/80 mg group, 93 (62.8%) of 148 patients in the 40/25 mg group and 93 (61.6%) of 151 patients in the standard therapy group. No apparent correlation was observed between the incidence of adverse events or adverse drug reactions and concomitant use of antitumor agents metabolized by CYP3A4.

The incidence of serious adverse events was not significantly different across the groups. No serious adverse event was considered by the investigator to be related to aprepitant. Serious adverse events led to the death of one patient in the standard therapy group and one in the 125/80 mg group. The former died of febrile neutropenia, acute respiratory distress syndrome

Table 2. Characteristics of patients

Characteristics	Aprepitant 125/80 mg + standard therapy (n = 146)	Aprepitant 40/25 mg + standard therapy (n = 143)	Standard therapy (n = 150)
Sex (%)			
Female	24.0	25.2	25.3
Male	76.0	74.8	74.7
Age (%)			
≥65 years	37.0	51.7	42.0
<65 years	63.0	48.3	58.0
Mean (SD)	60.5 (9.7)	63.3 (9.4)	62.2 (9.8)
Use of concurrent emetogenic chemotherapy† (% of patients)	17.8	15.4	20.0
Cisplatin dose (% of patients)			
<70	0.0	0.0	0.0
≥70, <80	41.8	42.0	46.7
≥80, <90	56.2	57.3	52.7
≥90, <100	0.0	0.0	0.0
≥100	2.1	0.7	0.7
Mean dose (mg/m^2)	76.9	76.9	76.2
Alcoholic drinks/week (at the time of informed consent) (% of patients)			
None	57.5	61.5	58.0
Several times per month	10.3	6.3	10.7
3–4 times per week	6.2	3.5	7.3
Almost every day	26.0	28.7	24.0
History of morning sickness (% of patients)	43.3	38.2	44.1
History of motion sickness (% of patients)	9.6	4.2	11.3
History of cisplatin chemotherapy (% of patients)	17.8	15.4	17.3
History of chemotherapy except cisplatin (% of patients)	19.9	24.5	18.7
History of CINV except cisplatin chemotherapy (% of patients)	41.4	37.1	42.9
Primary cancer diagnosis (% of patients)‡	(n = 150)	(n = 148)	(n = 151)
Respiratory	73.3	73.0	70.2
Urogenital	16.7	13.5	14.6
Digestive	4.0	5.4	4.6
Eyes/ears/nose/throat	3.3	4.7	7.3
Other	3.3	3.4	3.3

†Hesketh level ≥3; analysis population: full analysis set. ‡Analysis population: safety analysis set. SD, standard deviation.

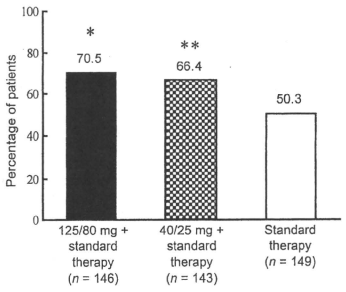

Fig. 2. Percentage of patients with a complete response (no emesis and no rescue therapy) in the overall phase (days–5) of aprepitant treatment. *P < 0.001 *versus* standard therapy group. **P < 0.01 *versus* standard therapy group.

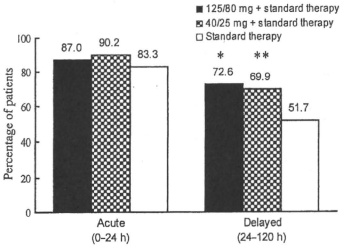

Fig. 3. Percentage of patients with a complete response (no emesis and no rescue therapy) in the acute phase (day 1) and the delayed phase (days 2–5). *P < 0.001 *versus* standard therapy group. **P < 0.01 *versus* standard therapy group.

(ARDS) and septic shock, and the latter died of cardiac failure. Neither case was considered to be related to aprepitant.

In addition, no clinically significant abnormality was observed in the vital signs, 12-lead electrocardiogram or body-weight in the aprepitant groups.

Discussion

As of October 2009 in Japan, 5-HT$_3$ receptor antagonist plus dexamethasone is the only standard antiemetic therapy for CINV. Approximately 25 and 50% of patients treated with highly emetogenic antitumor agents fail to respond to such therapy in the acute and delayed phases, respectively.[5] This study

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Table 3. Subgroup analysis of the percentage of patients with complete response over the course of treatment

	Patients with complete response (%)		
	Aprepitant 125/80 mg + standard therapy (n = 146)	Aprepitant 40/25 mg + standard therapy (n = 143)	Standard therapy (n = 149)
Sex			
Female	68.6	50.0	36.8
Male	71.2	72.0	55.0
Age (years)			
≥65 years	72.2	71.6	51.6
<65 years	69.6	60.9	49.4
History of cisplatin chemotherapy			
Yes	65.4	54.5	19.2
No	71.7	68.6	56.9

was conducted in Japanese cancer patients who received cancer chemotherapy including cisplatin at a dose of ≥70 mg/m^2 to evaluate the efficacy and safety of adding aprepitant to standard antiemetic therapy (5-HT$_3$ receptor antagonist and dexamethasone). It was shown that the percentage of patients with a complete response (the primary efficacy end-point) in the overall phase including both the acute (day 1) and delayed (days 2–5) phases was significantly higher in the aprepitant groups than in the standard therapy group, irrespective of sex, age or previous treatment with cisplatin. In the acute phase, the percentage of patients with a complete response was not significantly different between the aprepitant and the standard therapy groups. In the delayed phase as well as the overall phase, on the other hand, the percentage of patients with a complete response was significantly higher in the aprepitant groups. These results demonstrated the efficacy of aprepitant for CINV in the delayed phase, when 5-HT$_3$ receptor antagonist plus dexamethasone, the current standard antiemetic therapy in Japan, is not very effective. Although the percentage of patients with a complete response in the overall phase, the primary efficacy end-point, was significantly higher in both aprepitant groups (40/25 and 125/80 mg) than in the standard therapy group, the percentages of patients with "complete protection" and "no significant nausea" in the overall phase and delayed phase, which were secondary end-points, were statistically significantly higher only in the 125/80 mg group. In addition, the incidence or severity of adverse events was not markedly different between each aprepitant and standard therapy groups. Based on these results, the recommended dose of aprepitant is considered to be 125/80 mg (oral administration at a dose of 125 mg on day 1 and a dose of 80 mg on days 2–5) in Japanese cancer patients.

In the present study, unlike the overseas studies,[9,10] efficacy estimated using either the primary measure (the percentage of patients with complete response) or other secondary measures was not significantly greater in either aprepitant group in the acute phase. Nonetheless, the percentage of patients with a complete response (125/80 mg group, 87.0%; 40/25 mg group, 90.3%) in the acute phase in the present study was not inferior to that in overseas studies (89.2%,[9] 82.8%[10]). In this study, the percentage of patients with a complete response in the standard therapy group in the acute phase was substantially higher (83.3%) than in the overseas studies (78.1%,[9] 68.4%,[10]), indicating that the sample size was too small to detect any additional efficacy attributable to aprepitant for CINV in the acute phase.

In terms of safety, the incidence of adverse events was not different between the aprepitant and standard therapy groups, and the severity of adverse events was not markedly different across the groups. The incidence of serious adverse events was not significantly different across the groups, and no serious adverse event was considered by the investigator to be related to aprepitant. Since aprepitant has an inhibitory effect on CYP3A4, interactions between aprepitant and antitumor agents metabolized by CYP3A4 were a concern. Supporting overseas reports that failed to find notable interactions between aprepitant and docetaxel or vinorelbine,[17,18] the present study showed that the incidence of adverse events was not affected by combining aprepitant with antitumor agents metabolized by CYP3A4. These results showed that the safety of aprepitant is maintained irrespective of which metabolic pathways are disrupted by the antitumor agents.

It is known that aprepitant increases the plasma concentration of dexamethasone administered in combination,[19] and that this increase probably accounts for the higher incidence of serious infections such as febrile neutropenia associated with the concomitant use of aprepitant.[11] Therefore, in this study the dose of dexamethasone was adjusted so that comparable dexamethasone levels could be achieved in all groups. Population pharmacokinetic analysis of the plasma dexamethasone concentration found that aprepitant at doses of 125/80 mg and 40/25 mg reduced the clearance of dexamethasone to approximately 50% and 75%, respectively, of that in the absence of aprepitant in Japanese patients,[20] demonstrating the appropriateness of dose adjustment of dexamethasone in the present study. The appropriateness was also supported by data showing no increase in the incidence of serious infections such as febrile neutropenia in the aprepitant combination groups.

Table 4. Percentage of patients reaching efficacy end-points, by study phase and treatment group, using data obtained after dose adjustment

	Treatment group								
	Overall phase (0–120 h)			Acute phase (0–24 h)			Delayed phase (24–120 h)		
End-point	A 125/80	A 40/25	ST	A 125/80	A 40/25	ST	A 125/80	A 40/25	ST
Total no.	146	143	149	146	143	150	146	143	149
No emesis (%)	76.7*	74.1*	51.0	89.7	90.2	83.3	78.8*	77.6*	53.0
No rescue (%)	80.8	80.4	79.2	95.2	98.6	96.0	82.2	81.1	79.9
No nausea (%)	34.2	28.0	24.2	67.1	63.6	66.0	34.9	30.1	26.2
No significant nausea (%)	69.2	60.8	55.7	90.4	84.6	88.0	72.6**	60.8	56.4
Complete protection (%)	61.6**	53.1	43.0	83.6	80.4	82.0	65.1**	55.2	44.3
Total control (%)	33.6	28.0	24.2	66.4	63.6	64.7	34.2	30.1	26.2

*P < 0.001. **P < 0.01. A 125/80: standard therapy plus aprepitant 125 mg on day 1 and aprepitant 80 mg on days 2–5; A 40/25: standard therapy plus aprepitant 40 mg on day 1 and 25 mg on days 2–5; No nausea: nausea score 0; No significant nausea: nausea score 0 and 1; Complete protection: no emesis, no rescue therapy and no significant nausea (nausea score 0 and 1); Total control: no emesis, no rescue therapy and no nausea (nausea score 0). ST, standard therapy.

Table 5. Summary of adverse events

Percentage of patients	Treatment group		
	Aprepitant 125/80 mg + standard therapy (n = 150)	Aprepitant 40/25 mg + standard therapy (n = 148)	Standard therapy (n = 151)
With ≥1 adverse event	99.3	99.3	99.3
With drug-related adverse events†	23.3	18.9	19.9
With serious adverse events	6.0	6.8	2.6
Discontinued due to adverse events	0.7	1.4	0.0
With most common adverse events‡			
Anorexia	48.0	59.5	53.6
Constipation	38.7	42.6	45.7
Hiccups	43.3	33.1	37.1
Malaise	25.3	31.8	17.9
Diarrhea	21.3	26.4	26.5
Nausea	36.7	41.9	35.1
Vomiting	14.7	14.9	19.2
Pyrexia	9.3	12.8	13.9
Insomnia	4.7	7.4	10.6
With febrile neutropenia	4.0	4.1	6.6

†Determined by the investigator as possibly drug related, probably drug related or definitely drug related. ‡Incidence ≥10% in at least one group. There were no statistically significant ($P > 0.1$) differences in the risk of adverse events between the treatment groups. Statistical testing was not performed for individual common adverse events. Nausea and vomiting were considered adverse events if they occurred after day 5 of the study, or at any time if they were determined by the investigator to be serious or drug related, or if they resulted in discontinuation.

In conclusion, aprepitant used in combination with standard antiemetic therapy (5-HT_3 receptor antagonist and corticosteroid) was well tolerated and very effective in preventing CINV associated with highly emetogenic antitumor agents in Japanese cancer patients.

Trial members. Koichi Goto (protocol evaluation committee), Nobuyuki Yamamoto (protocol evaluation committee), Hiroshi Saito (protocol evaluation committee), Yoichi Nakanishi (protocol evaluation committee), Hiroyuki Iinuma (ECG committee), Chikuma Hamada (medical statistical adviser).

Principal investigators. Yuka Fujita (National Hospital Organization Dohoku National Hospital); Masahiro Yanase (Sunagawa City Medical Center); Koichi Yamazaki (Hokkaido University Hospital); Atsushi Taira (Sapporo Medical University Hospital); Satoshi Takahashi (Sapporo Medical University Hospital); Kenji Numahata (Tohoku University Hospital); Akira Inoue (Tohoku University Hospital); Masashi Tanaka (Miyagi Cancer Center); Tomonori Habuchi (Akita University Hospital); Yoshihiko Tomita (Yamagata University Hospital); Satoru Ishikawa (Hitachi General Hospital); Takefumi Saito (National Hospital Organization Ibaraki Higashi National Hospital); Hideyuki Akaza (Tsukuba University Hospital); Koji Kikuchi (Tsukuba Medical Center Hospital); Kiyoshi Mori (Tochigi Cancer Center); Yoshiki Ishii (Dokkyo Medical University Hospital); Ken-ichiro Yoshida (Dokkyo Medical University Hospital); Kazuhiro Suzuki (Gunma University Hospital); Shinichi Ishihara (National Hospital Organization, Nishigunma National Hospital); Kyoko Tanaka (National Hospital Organization Saitama National Hospital) Katsuhiko Aoyama (National Hospital Organization Higashi Saitama Hospital); Shuichi Yoneda (Saitama Cancer Center); Eishin Hoshi (Saitama Cardiovascular and Respiratory Center); Hidemitsu Funabashi (National Hospital Organization Chiba Medical Center); Tsutomu Numata (National Hospital Organization Chiba Medical Center); Yuichi Takiguchi (Chiba University Hospital); Tetsuro Moriya (Matsudo City Hospital); Toshio Yoshida (Nihon University Itabashi Hospital); Shigeo Horie (Teikyo University Hospital); Masahiro Tsuboi (Tokyo Medical University Hospital); Yoshikazu Hirano (The Fraternity Memorial Hospital); Kazuhiro Ishizaka (Kanto Central Hospital of the Mutual Aid Association of Public School Teachers); Ikuo Sekine (National Cancer Center Hospital); Takeshi Horai (The Cancer Institute Hospital of JFCR [Japanese Foundation for Cancer Research]); Akihiko Gemma (Nippon Medical School Hospital); Masahiko Shibuya (Tokyo Metropolitan Komagome Hospital); Yasuyuki Yoshizawa (Tokyo Medical and Dental University Hospital Faculty of Medicine); Tadashi Arai (Sempo Tokyo Takanawa Hospital); Tetsuo Sato (Jikei University Hospital); Masato Fujii (National Hospital Organization Tokyo Medical Center); Makoto Miyahara (Takagi Hospital); Shinichi Odama (Ome Municipal General Hospital); Shigeyuki Aoki (Showa General Hospital); Tomoyuki Yoshida (Tokyo Medical University Hachioji Medical Center); Akira Fujita (Tokyo Metropolitan Fuchu Hospital); Tomoyuki Goya (Kyorin University Hospital); Atsuhisa Tamura (National Hospital Organization Tokyo National Hospital); Haruhiko Kaguraoka (Higashi Yamato Hospital); Shigeru Minowada (International Medical Center of Japan); Takashi Ogura (Kanagawa Cardiovascular and Respiratory Center); Hiroshi Kunikane (Yokohama Municipal Citizen's Hospital); Junichi Ishitoya (Yokohama City University Medical Center); Kazumasa Noda (Kanagawa Cancer Center); Michiaki Narusima (Showa University Fujigaoka Hospital); Noriyuki Masuda (Kitasato University Hospital); Sumio Noguchi (Yokosuka Kyosai Hospital); Kenji Eguchi (Tokai University Hospital); Tetsuyuki Morikawa (Yokohama Rosai Hospital); Kunio Yamaguchi (Yokohama Rosai Hospital); Mamoru Tsukuda (Yokohama City University Hospital); Hirohisa Yoshizawa (Niigata University Medical and Dental Hospital); Akira Iwashima (Nagaoka Chuo General Hospital); Muneharu Maruyama (Toyama University Hospital); Kiyoshi Koshida (National Hospital Organization Kanazawa Medical Center); Kazuo Kasahara (Kanazawa University Hospital); Koichi Nishi (Ishikawa Prefectural Central Hospital); Masayoshi Shimamura (Ishikawa Prefectural Central Hospital); Kazuhiro Okafuji (Fukuiken Saiseikai Hospital); Keishi Kubo (Shinshu University Hospital); Sekiya Koyama (National Hospital Organization National Chushin-Matsumoto Hospital); Toshiyuki Sawa (Gifu Municipal Hospital); Jo Shindo (Ogaki Municipal Hospital); Takashi Kato (Shizuoka Red Cross Hospital); Kingo Chida (Hamamatsu University School of Medicine, University Hospital); Masakazu Takagi (Shizuoka General Hospital); Toshiaki Takahashi (Shizuoka Cancer Center); Yoshinori Hasegawa (Nagoya University Hospital); Toyoaki Hida (Aichi

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