sensitivity to chemotherapy, because they had DFI > 6 months. In a recent trial of recurrent ovarian cancer with DFI > 6 months, patients who received platinum-based chemotherapy with or without paclitaxel had a favorable prognosis; 29 and 24 months in median survival and around 20% in 5-year survival, respectively (Parmar et al., 2003). Though patients undergoing SCS using the new criteria of patient selection seem to have much better survival than patients receiving chemotherapy alone, our study was retrospective and non-comparative, and our data were based on a relatively small number of strictly selected patients. To provide solid evidence for the therapeutic benefit of SCS and to find better selection criteria for the surgery, further studies including randomized controlled studies are required.

REFERENCES

Bristow RE, Lagasse LD and Karlan BY (1996) Secondary surgical cytoreduction for advanced epithelial ovarian cancer. Patient selection and review of the literature. Cancer 78: 2049-2062

Conte PF, Sertoli MR, Bruzzone M, Rubagotti A, Rosso R, Bentivoglio G, Conio A and Pescetto G (1985) Cisplatin, methotrexate, and 5-fluorouracil combination chemotherapy for advanced ovarian cancer. Gynecol Oncol 20: 290-297

Cormio G, di Vagno G, Cazzolla A, Bettocchi S, di Gesu G, Loverro G and Selvaggi L (1999) Surgical treatment of recurrent ovarian cancer: report of 21 cases and a review of the literature. Eur J Obstet Gynecol Reprod Biol 86: 185-188

Delgado G, Oram DH and Petrilli ES (1984) Stage III epithelial ovarian cancer: the role of maximal surgical reduction. Gynecol Oncol 18: 293-298

Eisenkop SM, Friedman RL and Wang HJ (1995) Secondary cytoreductive surgery for recurrent ovarian cancer. A prospective study. Cancer 76: 1606-1614

Eisenkop SM, Friedman RL and Spirtos NM (2000) The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. Cancer 88: 144-153

Goldie JH and Coldman AJ (1979) A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 63: 1727-1733

Griffiths CT (1975) Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr 42: 101-104

Hacker NF, Berek JS, Lagasse LD, Nieberg RK and Elashoff RM(1983) Primary cytoreductive surgery for epithelial ovarian cancer. Obstet Gynecol 61: 413-420

Hainsworth JD, Grosh WW, Burnett LS, Jones HW, III, Wolff SN and Greco FA (1988) Advanced ovarian cancer: long-term results of treatment with intensive cisplatin-based chemotherapy of brief duration. Ann Intern Med 108: 165-170

Jänicke F, Holscher M, Kuhn W, von Hugo R, Pache L, Siewert JR and Graeff H(1992) Radical surgical procedure improves survival time in patients with recurrent ovarian cancer. Cancer 70: 2129-2136

Kaplan EL and Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457-481

Kawana K, Yoshikawa H, Yokota H, Onda T, Nakagawa K, Tsutsumi O and Taketani Y (1997) Successful treatment of brain metastases from ovarian cancer using gamma-knife radiosurgery. Gynecol Oncol 65: 357-359

Landoni F, Pellegrino A, Cormio G, Milani R, Maggioni A and Mangioni C (1998) Platin-based chemotherapy and salvage surgery in recurrent ovarian cancer following negative second-look laparotomy. Acta Obstet Gynecol Scand 77: 233-237

Louie KG, Ozols RF, Myers CE, Ostchega Y, Jenkins J, Howser D and Young RC (1986) Long-term results of a cisplatin-containing combination chemotherapy regimen for the treatment of advanced ovarian carcinoma. J Clin Oncol 4: 1579-1585

Munkarah A, Levenback C, Wolf JK, Bodurka Bevers D, Tortolero Luna G, Morris RT and Gershenson DM(2001) Secondary cytoreductive surgery for localized intra-abdominal recurrences in epithelial ovarian cancer. Gynecol Oncol 81: 237-241

Neijt JP, ten Bokkel Huinink WW, van der Burg ME, van Oosterom AT, Willemse PH, Heintz AP, van Lent M, Trimbos JB, Bouma J, Vermorken JB and van Hauwelingen JC (1987) Randomized trial comparing two combination chemotherapy regimens (CHAP-5 v CP) in advanced ovarian carcinoma. J Clin Oncol 5: 1157-1168

Norton L and Simon R (1977) Tumor size, sensitivity to therapy, and design of treatment schedules. Cancer Treat Rep 61: 1307-1317

Onda T, Yoshikawa H, Yasugi T, Mishima M, Nakagawa S, Yamada M, Matsumoto K and Taketani Y (1998) Patients with ovarian carcinoma upstaged to stage III after systematic lymphadenectomy have similar survival to Stage I/II patients and superior survival to other Stage III patients. Cancer 83: 1555-1560

Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB, Wheeler S, Swart AM, Qian W, Torri V, Floriani I, Jayson G, Lamont A, and Trope C (2003) Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 361: 2099-2106

Roberts WS (1996) Cytoreductive Surgery in Ovarian Cancer: Why, When, and How? Cancer Control 3: 130-136

Rose PG (2000) Surgery for recurrent ovarian cancer. Semin Oncol 27: No 3, Supple 7,

Scarabelli C, Gallo A and Carbone A (2001) Secondary cytoreductive surgery for patients with recurrent epithelial ovarian carcinoma. Gynecol Oncol 83: 504-512

Sijmons EA and Heintz AP (2000) Second-look and second surgery: second chance or second best? Semin Surg Oncol 19: 54-61

Sutton GP, Stehman FB, Einhorn LH, Roth LM, Blessing JA and Ehrlich CE(1989) Ten-year follow-up of patients receiving cisplatin, doxorubicin, and cyclophosphamide chemotherapy for advanced epithelial ovarian carcinoma. J Clin Oncol 7: 223-229

Tay EH, Grant PT, Gebski V and Hacker NF (2002) Secondary cytoreductive surgery for recurrent epithelial ovarian cancer. Obstet Gynecol 99: 1008-1013

Vaccarello L, Rubin SC, Vlamis V, Wong G, Jones WB, Lewis JL and Hoskins WJ (1995) Cytoreductive surgery in ovarian carcinoma patients with a documented previously complete surgical response. Gynecol Oncol 57: 61-65

Vogl SE, Pagano M, Kaplan BH, Greenwald E, Arseneau J and Bennett B (1983) Cis-platin based combination chemotherapy for advanced ovarian cancer. High overall response rate with curative potential only in women with small tumor burdens.

Zang ZT, Chen J, Tang MQ, Liu Q and Cai SM (2000) Effect of cytoreductive surgery on survival of patients with recurrent epithelial ovarian cancer. J Surg Oncol 75: 24-30

Zang RY, Li ZT, Tang J, Cheng X, Cai SM, Zhang ZY and Teng NN(2004) Secondary cytoreductive surgery for patients with relapsed epithelial ovarian carcinoma: who benefits? Cancer 100: 1152-1161

FIGURE LEGENDS

Figure 1. Survival of all 44 patients who underwent secondary cytoreductive surgery.

Figure 2. Outcome of secondary cytoreductive surgery and survival. Survival of the patients with largest residual tumors 0cm, <1cm, ≥1cm is shown in solid black, solid gray and dotted black line, respectively. The difference of survival is statistically significant (p=0.0007, Log-rank). There is no statistical difference in survival between patients with residual tumors <1cm and ≥1cm (p=0.1314, Log-rank).

Figure 3. Comparison in survival between patients having one or two favorable prognostic factors (Group 1/2) and three or four favorable factors (Group 3/4). Survival of patients in Group 3/4 and Group 1/2 is shown as a solid black or solid gray line, respectively. Patients in Group 3/4 had significantly better survival compared with patients in Group 1/2 (p<0.001, Log-rank).

Figure 4. Survival in relation to SCS outcome and number of favorable prognostic factors. Survival of patients in Group 3/4 are shown as solid lines. Solid black line and solid gray line show the survival of patients with no residual tumor and residual tumor at secondary cytoreductive surgery, respectively. Survival of patients in Group 1/2 are shown as dotted lines. Dotted black line and dotted gray line show the survival of patients with no residual tumor and any residual tumor at secondary cytoreductive surgery, respectively.

Table 1 Univariate analyses for variables during primary treatment

Variables	Number	Median survival (months)	p value
Peritoneal tumor spread			
Localized to the pelvis	10	NA	
Extended beyond the pelvis	34	29	0.039
Stage			
I/II	5	NA	
III/IV	39	29	0.045
Aortic lymph node metastases			
Absent	25	64	
Present	14	27	
Not assessed	5	25	0.009
Pelvic lymph node metastases			
Absent	20	47	
Present	21	32	
Not assessed	3	25	0.126
Systematic lymphadenectomy			
Not performed	3	25	
Pelvic only	7	29	
Pelvic and Aortic	34	33	0.296
Histology			
Serous	35	37	
Others	9	23	0.197
Residual tumor at PCS*			
0	34	32	
Any	10	40	0.961

*PCS: Primary cytoreductive surgery

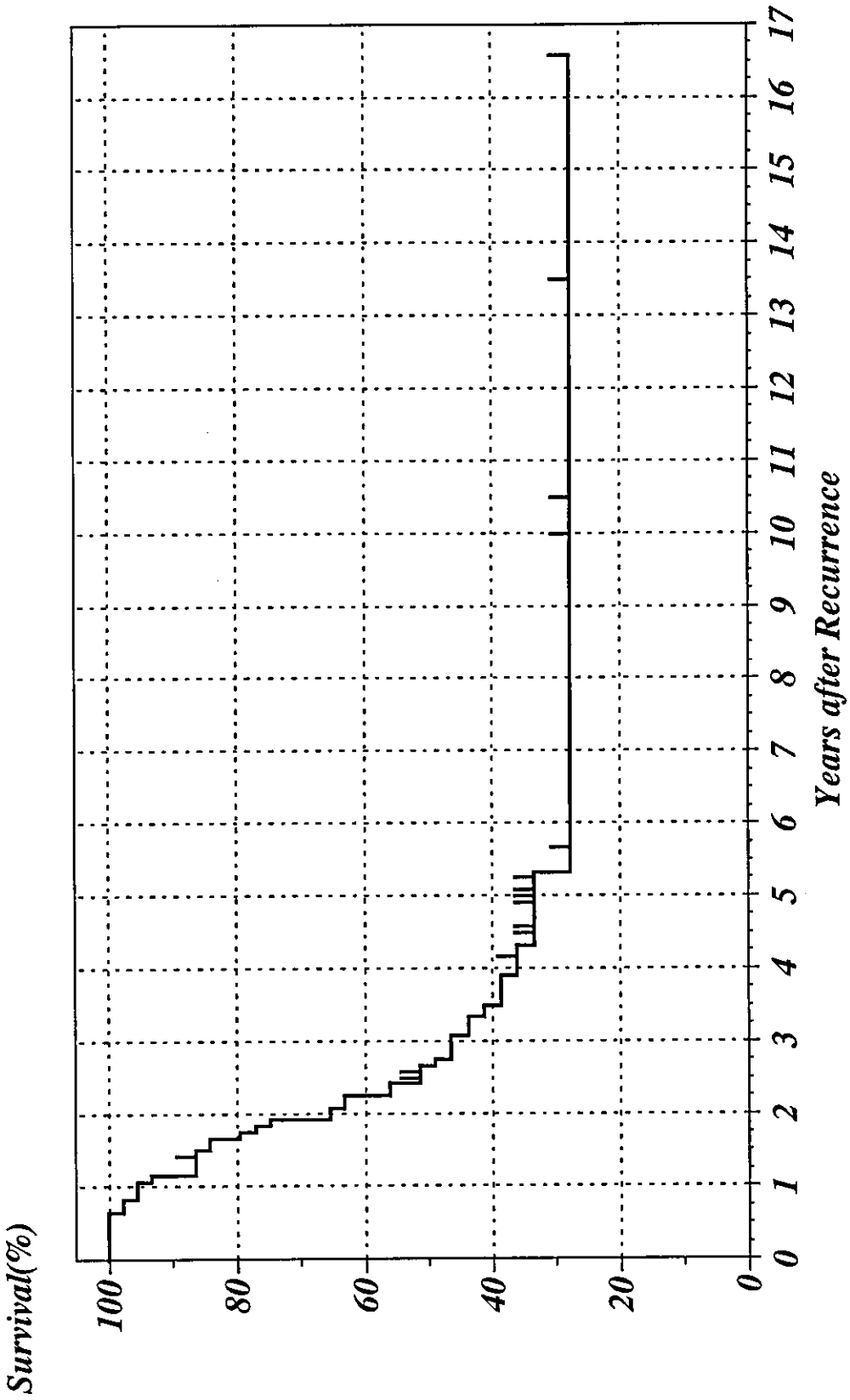
Table 2 Univariate analyses for variables at recurrence

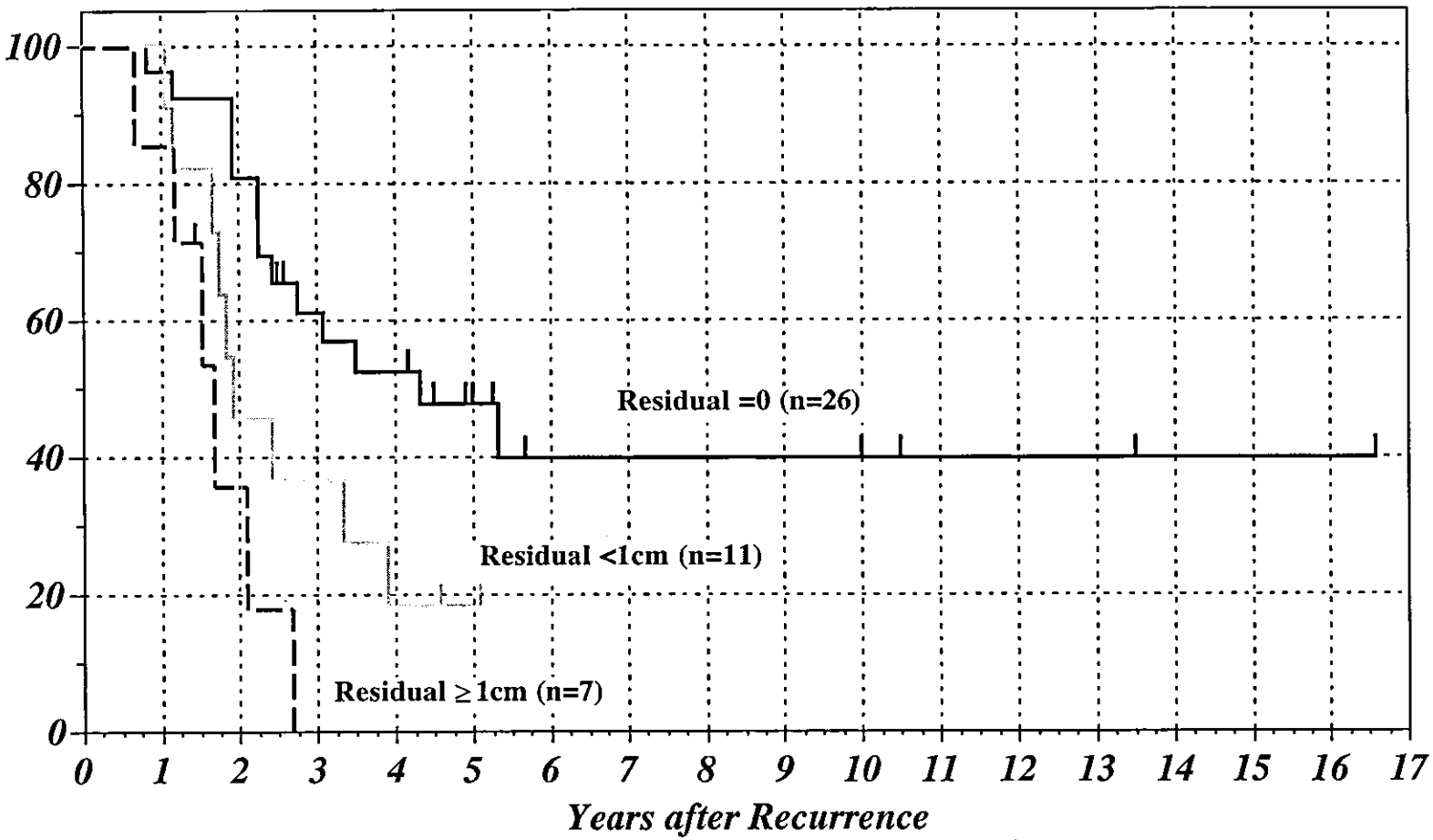
Variables	Number	Median survival (months)	p value
Age at recurrence			
<50	17	29	
≥50	27	40	0.860
Disease-free interval			
≥12M	31	47	
<12M	13	23	0.002
Intraperitoneal tumor			
Absent	12	64	
Present	32	27	0.117
Pelvic or aortic lymph node metastases			
Absent	34	32	
Present	10	37	0.419
Distant metastasis			
Absent	38	32	
Present	6	40	0.496
Liver metastasis			
Absent	42	33	
Present	2	20	0.005
No. of recurrent tumors			
Solitary	16	64	
Multiple	28	27	0.007
Size of maximum tumor			
<6cm	38	40	
≥6cm	6	14	<0.001
Massive ascites(>500ml)			
Absent	41	33	
Present	3	32	0.318
Performance status			
0 to 2	42	29	
3	2	42	0.746
Presurgical chemotherapy			
Not done	23	33	
Done	21	29	0.677
Bowel resection			
Not done	33	33	
Done	11	27	0.650
Residual tumor at SCS			
0	26	52	
Any	18	22	0.002

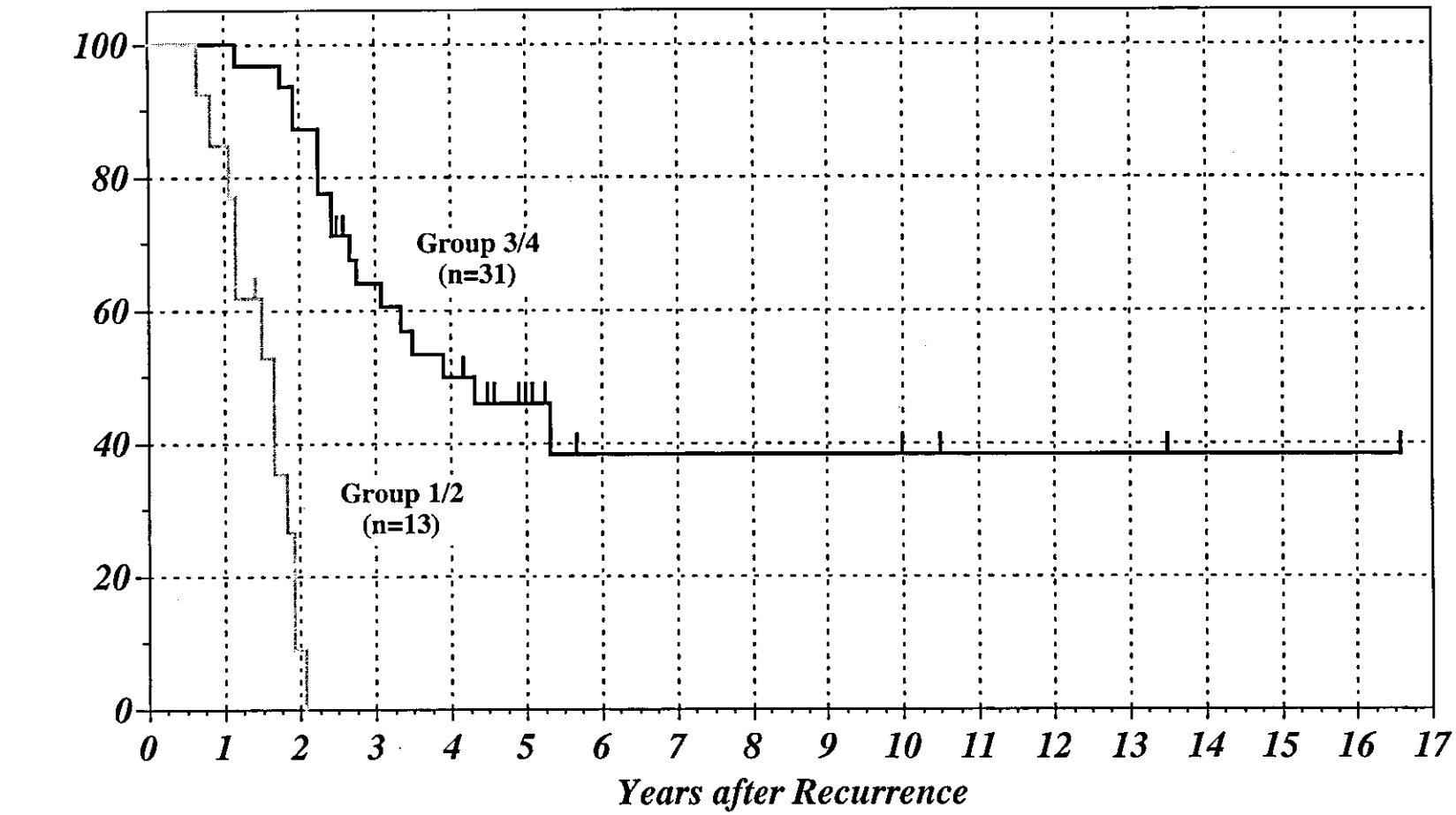
Table 3 Multivariate analysis using the seven prognostic variables in the univariate analyses

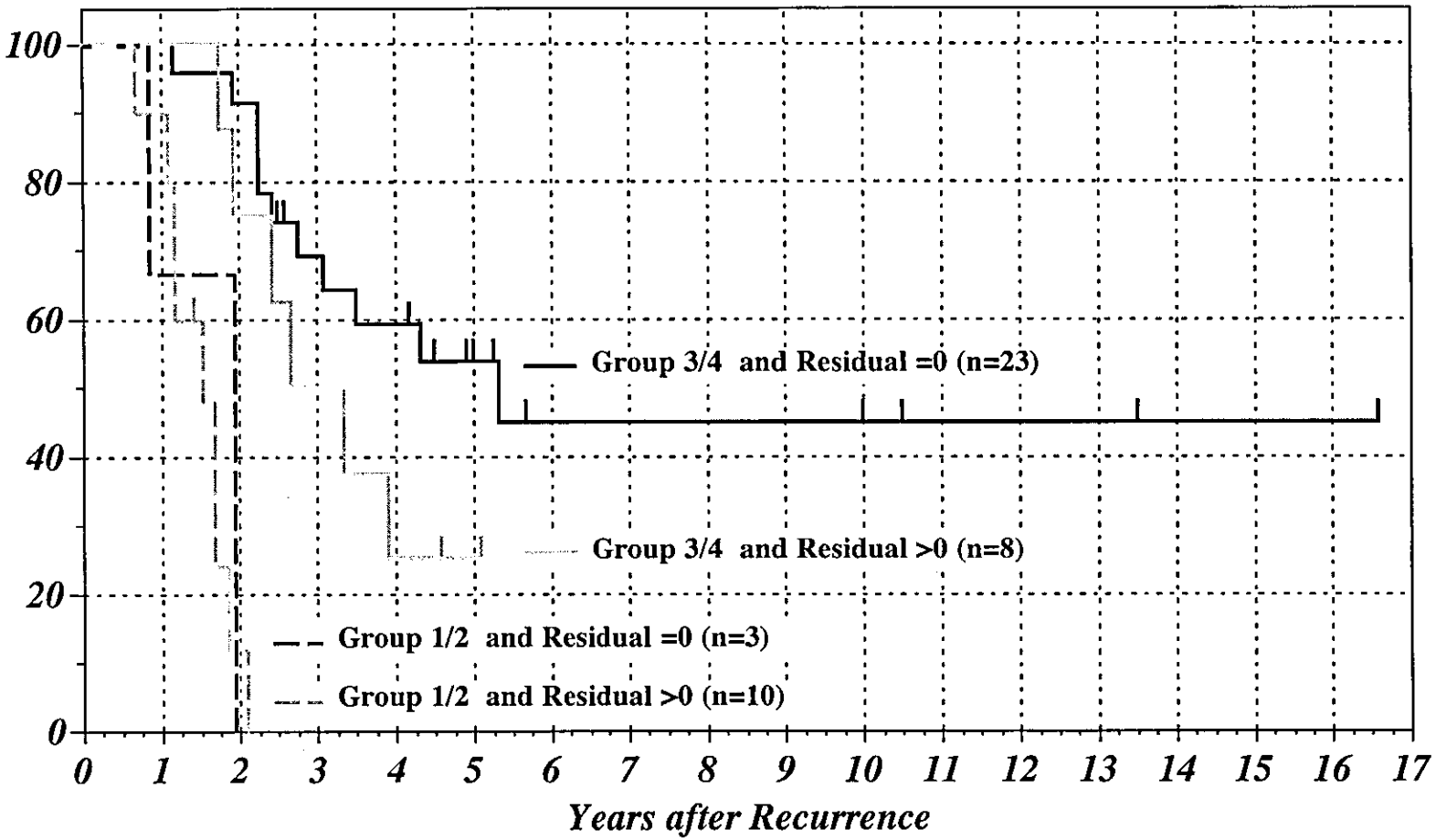
Variables	Multivariate analysis	
	Risk ratio (95%CI)	p value
Peritoneal tumor spread at PCS*		
Localized to the pelvis	1.00	
Extended beyond the pelvis	0.80 (0.42-1.76)	0.540
Stage		
I/II	1.00	
III/IV	0.90 (0.22-5.60)	0.893
Aortic lymph node metastases at PCS*		
Absent	1.00	
Present	1.23 (0.56-2.64)	
Not assessed	1.78 (0.61-5.33)	0.088
Disease-free interval		
≥12M	1.00	
<12M	2.45 (1.11-5.39)	0.027
Liver metastasis		
Absent	1.00	
Present	4.00 (1.40-10.03)	0.013
No. of recurrent tumors		
Solitary	1.00	
Multiple	3.73 (1.79-9.58)	<0.001
Size of maximum tumor		
<6cm	1.00	
≥6cm	7.43 (3.12-18.92)	<0.001

*PCS: Primary cytoreductive surgery


Survival(%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Years after Recurrence


Survival(%)
100
80
60
40
20
0
Residual =0 (n=26)
Residual <1cm (n=11)
Residual ≥1cm (n=7)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Years after Recurrence


Survival(%)
100
80
60
40
20
0
Group 3/4
(n=31)
Group 1/2
(n=13)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Years after Recurrence


Survival(%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Years after Recurrence
Group 3/4 and Residual =0 (n=23)
Group 3/4 and Residual >0 (n=8)
Group 1/2 and Residual =0 (n=3)
Group 1/2 and Residual >0 (n=10)

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Clinical Trial Note

Feasibility Study of Neoadjuvant Chemotherapy Followed by Interval Cytoreductive Surgery for Stage III/IV Ovarian, Tubal and Peritoneal Cancers: Japan Clinical Oncology Group Study JCOG0206

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A feasibility study was started in January 2003 on neoadjuvant chemotherapy (NAC) followed by interval cytoreductive surgery (ICS) and postoperative chemotherapy for stage III/IV müllerian carcinomas such as ovarian, tubal and peritoneal carcinomas. The purpose is to assess the safety and efficacy of the treatment starting with NAC and also to know whether we can accurately diagnose these advanced carcinomas by imaging studies, cytologic findings and tumor markers without staging laparotomy or laparoscopy. Fifty-six patients with advanced müllerian carcinomas will be recruited to the study. After confirmation of diagnosis by laparoscopic inspection and biopsies, patients undergo four cycles of chemotherapy as NAC, followed by ICS and an additional four cycles of post-surgical chemotherapy. The primary endpoint is proportion of clinical complete remission after accomplishment of the protocol treatment, while the major secondary endpoint is positive predictive value of diagnosis before laparoscopy regarding tumor origin, histology and stage. Based on the results of this study, we will conduct a phase III study to compare the treatment starting with NAC and primary cytoreductive surgery followed by post-surgical chemotherapy.

Key words: ovarian neoplasms – laparoscopy – neoadjuvant therapy – interval cytoreductive surgery

INTRODUCTION

Prognosis of patients with advanced epithelial ovarian, tubal and peritoneal carcinomas is known to be poor. Even using platinum compound regimens, the 5-year survival rate of stage III/IV ovarian cancer is still around 20% (1). The current standard treatment for advanced ovarian cancer is primary cytoreductive surgery followed by post-surgical chemotherapy. However, optimal cytoreduction in primary surgery can be achieved only in 40% of stage III/IV ovarian cancer patients (2). An alternative to primary surgical cytoreduction in patients with unresectable bulky tumors or poor performance status is the use of chemotherapy in the neoadjuvant setting. Recent retrospective analyses (3–6) have revealed that progression-free and overall survival were comparable between patients treated with neoadjuvant chemotherapy (NAC) followed by interval cytoreductive surgery (ICS) and those treated by primary cytoreductive surgery, though the former group was older and had a poorer performance status. Phase II and III trials have not been performed on the role of neoadjuvant-setting treatment for advanced ovarian, tubal and peritoneal cancers. Therefore, we started a phase II study to assess the safety and efficacy of NAC followed by ICS and post-surgical chemotherapy before comparing with the current standard treatment including primary cytoreductive surgery in randomized controlled trial. Neoadjuvant setting has the advantage of earlier treatment start and lower invasiveness. However, according to the current general rules for the management of ovarian cancer, it is neces-

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sary to confirm the origin, histology and stage before starting treatment by staging laparotomy or laparoscopy. Thus, we also determine whether we can omit the 'extra procedure' of staging laparotomy or laparoscopy before the neoadjuvant-setting treatment in the majority of patients with advanced ovarian, tubal or peritoneal cancer.

The study protocol was designed by Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG), approved by the Clinical Trial Review Committee of JCOG on December 6, 2002, and activated on January 14, 2003.

PROTOCOL DIGEST OF THE JCOG0206

PURPOSE

The purposes are to assess the safety and efficacy of the treatment starting with NAC with paclitaxel and CBDCA for phase III study, comparing NAC therapy with current standard procedure, and to know whether we can accurately diagnose these advanced carcinomas by imaging studies, cytologic findings and tumor markers without staging laparotomy or laparoscopy.

STUDY SETTING

A multi-institutional (26 centers) non-randomized phase II trial.

RESOURCES

Health Sciences Research Grants for Clinical Research for Evidenced Based Medicine and Grants-in Aid for Cancer Research (nos 14S-4, 14-12), from the Ministry of Health, Labor and Welfare, Japan.

ENDPOINTS

Primary endpoint is proportion of clinical complete remission (%cCR) among all stage III or IV müllerian carcinoma confirmed by laparoscopic inspection and histopathology of biopsy specimens. Clinical complete remission is defined as disappearance of all lesions by computed tomography (CT) or magnetic resonance imaging (MRI), no pleural effusions by chest radiography and normal serum CA125 level (<20 U/ml) after completion of the protocol treatment.

Secondary endpoints are as follows: (i) positive predictive value (PPV) of pre-laparoscopic diagnosis concerning the origin and histology—proportion of the patients diagnosed as müllerian carcinoma by laparoscopic inspection and histopathology of biopsy specimen among those diagnosed by pre-laparoscopic findings; (ii) PPV of prelaparoscopic diagnosis concerning clinical stage—proportion of the patients diagnosed as stage III or IV by laparoscopic inspection among those diagnosed by pre-laparoscopic findings; (iii) PPV of overall pre-laparoscopic diagnosis—proportion of the patients diagnosed as stage III or IV müllerian carcinoma by laparoscopic inspection and histopathology of biopsy specimen among those diagnosed by pre-laparoscopic findings.

Other secondary endpoints are: (iv) response rate to NAC among patients whose clinical diagnosis is confirmed by laparoscopy; (v) proportion of patients who received ICS among patients whose clinical diagnosis is confirmed by laparoscopy; (vi) progression-free survival among patients whose clinical diagnosis is confirmed by laparoscopy; (vii) operative morbidity among all enrolled patients; (viii) adverse events among all enrolled patients: and (ix) overall survival among all enrolled patients.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

The study subjects are patients diagnosed as stage III or IV müllerian carcinoma by pre-laparoscopic clinical findings including imaging studies (CT, MRI or ultrasonography) and cytology of ascites, pleural effusions or fluids obtained by tumor centesis. Malignancies of other origins, such as breast and digestive tract, should be excluded by endoscopy, opaque enema or ultrasonography when these malignancies are suspected from symptoms, physical examination or imaging diagnosis. To rule out malignancy of digestive tract origin, criteria for tumor markers are set to be CA125 >200 U/ml and CEA <20 ng/ml.

Further inclusion criteria are: (i) clinically deemed to be a candidate for debulking surgery without evidence of brain, bone, bone marrow metastases, multiple lung or multiple liver metastases; (ii) presence of at least one measurable lesion; (iii) previously untreated for these malignancies and no history of treatment with chemotherapy nor radiotherapy even for other diseases; (iv) age 20–75 years; (v) Eastern Cooperative Oncology Group (ECOG) performance status of 0–3; (vi) adequate bone marrow, hepatic, renal, cardiac and respiratory functions; and (vii) written informed consent.

EXCLUSION CRITERIA

These are: (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ; (ii) pregnant or nursing; (iii) severe mental disorders; (iv) systemic and continuous use of steroidal drugs; (v) active infections; (vi) uncontrolled hypertension; (vii) diabetes mellitus, uncontrolled or controlled with insulin; (viii) history of cardiac failure, unstable angina, myocardial infarction within 6 months prior to the registration; (ix) liver cirrhosis or bleeding tendency contraindicating debulking surgery; (x) intestinal occlusion necessary for surgical treatment; and (xi) hypersensitivity to alcohol.

TREATMENT METHODS

DIAGNOSTIC LAPAROSCOPY

After enrolment, diagnostic laparoscopy is performed within 2 weeks. To confirm pre-laparoscopic clinical diagnosis of origin, histology and stage, inspection of peritoneal cavity and biopsy from the main tumor or metastatic tumors are per-

formed. Resection of any organs or tumors attempting to reduce tumor volume is not allowed.

NEOADJUVANT CHEMOTHERAPY (NAC)

Four cycles of combination of paclitaxel (175 mg/m^2, day 1) and carboplatin (AUC = 6, day 1) are administered every 3 weeks. NAC is initiated within 1 week after laparoscopy.

INTERVAL CYTOREDUCTIVE SURGERY (ICS)

ICS is performed in 4–7 weeks after administration of the fourth cycle of NAC unless disease progression occurs during NAC. Standard procedures of ICS consist of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and maximal debulking of metastatic tumors. Systematic pelvic and/or aortic lymphadenectomies are allowed, but not included in standard procedures.

POST-SURGICAL CHEMOTHERAPY

An additional four cycles of chemotherapy (same regimen as NAC) is administered (eight cycles of chemotherapy in total). Post-surgical chemotherapy is initiated within 3 weeks after ICS.

STUDY DESIGN AND STATISTICAL METHODS

The study is planned as a single-stage safety and efficacy study. Sample size calculation was primarily based on binominal test for the primary endpoint, %cCR. Forty-four eligible patients are required when expected %cCR of 40% and an acceptable lowest %cCR of 20% with alpha error level of 0.05 and beta error level of 0.1. Additionally, PPV is to be confident enough to omit laparoscopy before NAC in the following phase III study. It is not possible to use sensitivity or specificity to evaluate accuracy of clinical diagnoses, because laparoscopy is performed only in patients diagnosed as stage III/IV müllerian carcinomas by clinical findings in this study setting. Thus, Bayesian monitoring PPV is planned, which requires 56 patients to have the 10% or lower Bayesian posterior probability that PPV is <90% in case of three false positive patients assuming prior distribution of beta (9,1). The target sample size was determined to be 56, which also can be expected sufficient for primary endpoint. The planned accrual period is 1 year and the follow-up period is set as 3 years after the completion of accrual.

STUDY MONITORING

In-house interim monitoring is performed by the JCOG Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress according to the JCOG standard procedures. The monitoring reports are submitted to the JCOG Data and Safety Monitoring Committee every 6 months.

PARTICIPATING INSTITUTIONS

Hokkaido University, Sapporo Medical University, Tohoku University, University of Tsukuba, Gunma Prefectural Cancer Center, Shinshu University, National Defense Medical College, Saitama Cancer Center, National Cancer Center Hospital, The Jikei University School of Medicine, Cancer Institute Hospital, University of Tokyo, Juntendo University, Nagaoka Red Cross Hospital, Aichi Cancer Center, National Nagoya Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kinki University, Niigata Cancer Center, Kure National Hospital (Chugoku District Cancer Center), National Shikoku Cancer Center, National Kyushu Cancer Center, University of Kurume, Kyushu University, Saga Medical School and Kagoshima City Hospital.

References

1. Nguyen HN, Averette HE, Hoskins W, Sevin BU, Penalver M, Steren A. National survey of ovarian carcinoma. VI. Critical assessment of current International Federation of Gynecology and Obstetrics staging system. *Cancer* 1993;72:3007–11.
2. Covens AL. A critique of surgical cytoreduction in advanced ovarian cancer. *Gynecol Oncol* 2000;78:269–74.
3. Jacob JH, Gershenson DM, Morris M, Copeland LJ, Burke TW, Wharton JT. Neoadjuvant chemotherapy and interval debulking for advanced epithelial ovarian cancer. *Gynecol Oncol* 1991;42:146–50.
4. Onnis A, Marchetti M, Padovan P, Castellan L. Neoadjuvant chemotherapy in advanced ovarian cancer. *Eur J Gynaecol Oncol* 1996;17:393–6.
5. Schwartz PE, Rutherford TJ, Chambers JT, Kohorn EI, Thiel RP. Neoadjuvant chemotherapy for advanced ovarian cancer: long-term survival. *Gynecol Oncol* 1999;72:93–9.
6. Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, van Dam P. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. *Gynecol Oncol* 1998;71:431–6.

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Cisplatin, Paclitaxel and Escalating Doses of Doxorubicin (TAP) in Advanced Ovarian Cancer: a Phase I Trial

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Background: The objectives of this phase I trial were to determine the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II/III trials of doxorubicin (DOX) combined with paclitaxel (PTX) and cisplatin (CDDP) in patients with advanced ovarian cancer (AOC).
Methods: Twenty-eight patients with stage III/IV AOC received fixed doses of PTX (110 mg/m^2 over 24 h on day 1) and CDDP (75 mg/m^2 on day 2) and an escalating dose of DOX (20, 30, 40 or 50 mg/m^2 on day 1) every 3 weeks. The patients received up to six cycles of chemotherapy. At level 1, one of the original dose-limiting toxicities (DLTs), grade (G) 4 neutropenia lasting for 4 days or longer, occurred in four of six patients. The criterion for DLT was amended to 'G4 neutropenia lasting for 8 days or longer accompanied with G4 leukopenia' and four additional patients were evaluated at level 1.
Results: According to the new criteria, DLT was observed only in one of nine patients except one ineligible patient at level 1and two of six patients at level 4. G4 neutropenia and G4 leukopenia occurred in 85% and 44%, respectively, in the first course of chemotherapy. Non-hematological toxicity was generally mild or moderate. MTD was not determined at the planned dose levels. A clinical response was observed in 16 of 19 (84%) evaluable patients. Further dose escalation was not performed and RD was determined as level 4 because more than 30% of cycles required some modification of chemotherapy at level 4.
Conclusion: The combination of TAP including 50 mg/m^2 of DOX is feasible and well tolerated as first line chemotherapy in AOC, warranting further study of this regimen.

Key words: ovarian cancer – chemotherapy – doxorubicin – phase I study

INTRODUCTION

Since randomized trials have demonstrated the superiority of paclitaxel (PTX) plus cisplatin (CDDP) over cisplatin plus cyclophosphamide (CPA) in overall survival and progression-free survival (1,2) and subsequent trials demonstrated similar activity of PTX plus carboplatin (CBDCA) compared with PTX plus CDDP (3), the combination regimen of PTX plus platinum, such as CDDP or CBDCA, is considered the standard regimen for advanced ovarian cancer (AOC). The two-drug combination regimen of PTX and platinum yields a high response rate and improved survival for patients with AOC. In spite of chemotherapy development, the 5-year survival of patients with stage III/IV ovarian cancer is generally less than or around 20% (4), which is far from satisfactory. Therefore, several approaches, especially new agents or new drug combinations, are being examined in clinical studies to improve further the outcome of treatment for AOC.

Doxorubicin (DOX), an anthracycline, is known to be an active agent for ovarian cancer and was used in combination with CDDP and CPA as a standard regimen for ovarian cancer before the introduction of PTX plus platinum. The benefit of

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adding DOX to CDDP and CPA was controversial. A phase III randomized trial of CDDP plus CPA with or without DOX conducted by the Gynecological Oncology Group (GOG) (5) showed no clear benefit of DOX in the pathological complete response rate and median survival time. However, three meta-analyses demonstrated that the incorporation of DOX into the CDDP-based regimen for ovarian cancer may improve the long-term survival of AOC by 7–10% (6–8). Therefore, the value of DOX in the treatment of ovarian cancer was re-examined.

The benefit of adding DOX to the current standard regimen, PTX and platinum, should be evaluated to improve further the outcome of patients with AOC. To evaluate the safety and efficacy of this combination regimen, we conducted a phase I trial in patients with AOC for first-line chemotherapy using a combination of fixed doses of CDDP and PTX with escalating doses of DOX given every 3 weeks.

PATIENTS AND METHODS

Selection of Patients

The subjects of this study were untreated patients with stage IIIC or IV epithelial ovarian cancer. The histology of tumors included serous, mucinous, endometrioid, clear cell, mixed epithelial, undifferentiated, malignant Brenner, transitional cell and unclassified types. Patients with low potential malignancies were not included.

Other eligible criteria for entry into this study were as follows: (a) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (b) age 16–75 years; (c) adequate bone marrow function [white blood cell count (WBC) $\geq$3000/mm^3 or absolute neutrophil count (ANC) $\geq$1500/mm^3 and platelet count $\geq$100 000/mm^3], adequate hepatic function [total serum bilirubin $\leq$1.5 mg/dl and serum aspartate aminotransferase (AST) $\leq$2.5 times the upper limit of normal], adequate renal function (serum creatinine $\leq$1.5 mg/dl and creatinine clearance $\geq$50 ml/min) and adequate cardiac function (normal or minor deviation in electrocardiogram); and (d) written informed consent. Patients were ineligible if they had (a) severe mental disorders; (b) uncontrolled hypertension; (c) history of cardiac failure, unstable angina, myocardial infarction within 6 months prior to the study; (d) liver cirrhosis; (e) diabetes mellitus, controlled with insulin; (f) history of severe hypersensitivity or hypersensitivity to drugs formulated with polyoxyethylated castor oil (Cremophor EL) as an ingredient (e.g. cyclosporine or vitamin K); (g) hepatitis B e antigen (HBeAg) or antibody against hepatitis C virus (HCV); or (h) if they were pregnant.

Treatment Plan

All patients underwent staging laparotomy and, simultaneously, maximum cytoreductive surgery. Following surgery, eligible patients were enrolled into the study. Patients received up to six cycles of chemotherapy consisting of paclitaxel (PTX), doxorubicin (DOX) and cisplatin (CDDP). DOX was administered as a 30 min intravenous (IV) infusion on day 1. PTX was administered as a 24 h continuous i.v. infusion on day 1 following DOX administration. CDDP was administered as a 2 h i.v. infusion on day 2. Chemotherapy was repeated every 21 days, assuming recovery from the toxicity of the previous cycle. Four different dose levels were tested. The dose of DOX was escalated from 20 mg/m^2 (level 1) to 50 mg/m^2 (level 4) in increments of 10 mg/m^2 in sequential cohorts and doses of PTX and CDDP were fixed at 110 and 75 mg/m^2, respectively.

A pre-medication schedule consisted of a 20 mg intravenous dexamethasone infusion 12 and 6 h before chemotherapy, 50 mg oral diphenhydramine and 50 mg intravenous ranitidine administration 30 min before chemotherapy. No primary granulocyte colony-stimulating factor (G-CSF) prophylaxis was allowed. G-CSF use was allowed only when grade 4 leukopenia (<1000/m^3) or grade 4 neutropenia (<500/m^3) lasting for 3 days or longer or grade 2 fever ($\geq$38°C) during grade 3 leukopenia (<2000/m^3) or grade 3 neutropenia (<1000/m^3) was observed.

Treatment Modification

Re-treatment was delayed until the following criteria were met. (a) WBC $\geq$2500/mm^3 and platelet count $\geq$100 000/mm^3; (b) total serum bilirubin $\leq$1.5 mg/dl, serum AST $\leq$2.5 times the upper limit of normal and serum creatinine $\leq$1.5 mg/dl; (c) more than 48 h passed after the final G-CSF use; and (d) absence of active infection. Patients were taken out of the study if the treatment interval exceeded 42 days.

For patients experiencing any of the following toxicities, the doses of all three drugs were reduced to 90% of the previous dose: (a) grade 4 leukopenia (<1000/m^3); (b) grade 2 fever ($\geq$38°C) lasting for 3 days and/or bacteremia during grade 3 leukopenia (<2000/m^3) or neutropenia (<1000/m^3); (c) grade 3 thrombocytopenia (<50 000/m^3); and (d) grade 3 or 4 non-hematological toxicities other than nausea and vomiting. Toxicities were graded according to the Japan Clinical Oncology Group (JCOG) toxicity criteria (9), based on Common Toxicity Criteria of the National Cancer Institute (NCI-CTC, 1982) to extend and supplement the criteria.

Chemotherapy was discontinued if (a) response was revealed to be no change (NC) after three cycles of chemotherapy, (b) progressive disease (PD) was observed, (c) unacceptable toxicities were observed or (d) recovery from toxicities was prolonged.

Determination of Maximum Tolerated Dose and Recommended Dose

The primary objectives of the study were to determine the maximum tolerated dose (MTD) and the recommended dose (RD) of DOX when combined with 110 mg/m^2 of PTX and 75 mg/m^2 of CDDP. Initially, six patients were sequentially enrolled into the lowest dose level. Dose-limiting toxicity

(DLT) was evaluated in the first course of chemotherapy to determine MTD and in all courses of chemotherapy to determine the RD. If none or one of the six patients experienced DLT, then the following six patients would be enrolled into the next dose level. If four or more of the six patients experienced DLT and the dose level was higher than level 1, MTD was determined as the previous dose level. If two or three of the six patients experienced DLT, then an additional six patients would be enrolled into the same dose level at other than level 4. If three or fewer of 12 patients experienced DLT, then the next six patients would be enrolled into the next dose level. If four or more of 12 patients experienced DLT, then MTD was determined as that dose level. These steps were repeated until MTD was determined. RD was determined taking into account the DLT observed in the following courses of chemotherapy.

DLT was initially defined as (a) grade 4 leukopenia ($<1000/m^3$) or grade 4 neutropenia ($<500/m^3$) lasting for 4 days or longer; (b) grade 2 fever ($\geq 38°C$) lasting for 3 days and/or bacteremia during grade 3 leukopenia ($<2000/m^3$) or neutropenia ($<1000/m^3$); (c) grade 4 thrombocytopenia ($<25\,000/m^3$); and (d) grade 3 or 4 non-hematological toxicities other than nausea and vomiting. The criteria were subsequently amended as described in the next subsection.

Amendment of Criteria for Dose-limiting Toxicity

Among six patients enrolled into dose level 1, grade 4 neutropenia lasting for 4 days or longer [criterion (a)] was observed in four patients during the first course of chemotherapy and neutrophils were not counted in one patient with grade 2 leukopenia. Therefore, the study was discontinued and the toxicities were evaluated. Grade 4 neutropenia was observed for 6–7 days in three patients and observed for 11 days in one patient, although grade 4 leukopenia was not observed. However, all six patients recovered from the toxicity and could receive the subsequent course of chemotherapy without delay. No other DLT was observed in these six patients during the first and subsequent courses. Therefore, dose level 1 was evaluated to be safe and criterion (a) was considered to be too strict. Moreover, many phase I studies for ovarian cancer adopted a criterion of 'grade 4 neutropenia lasting for 8 days or longer' (10–14). Taken together, the following amendment of criteria and study design was permitted by the Data and Safety Monitoring Committee. (1) Criterion (a) was modified to 'grade 4 neutropenia lasting for 8 days or longer accompanied by grade 4 leukopenia for at least 1 day during the period'. According to this amendment, none of the above-mentioned four patients met the criterion. (2) A patient whose neutrophils were not counted was determined to be ineligible. (3) An additional four patients would be enrolled to dose level 1 to determine the safety of the dose level. If DLT was observed in none or one of nine patients, the subsequent patients would be enrolled at dose level 2. If DLT was observed in two of nine patients, an additional three patients would be enrolled at dose level 1. If DLT was observed in three or four of nine patients, the study would be discontinued.

Response Evaluation

A secondary objective of the study was to evaluate the efficacy of the TAP regimen. The World Health Organization (WHO) criteria (15) were employed in this study. Complete response (CR) was defined as the disappearance of all gross evidence of disease for at least 4 weeks. Partial response (PR) was defined as a $\geq 50\%$ reduction in the sum of the products of the two largest perpendicular dimensions of all two-dimensionally measurable lesions and no evidence of new lesions for at least 4 weeks. No change (NC) was defined as a $<25\%$ increase or a $<50\%$ reduction in the sum of the aforementioned products and no evidence of new lesions for at least 4 weeks. Progressive disease (PD) was defined as a $\geq 25\%$ increase in the sum of the above-mentioned products or the appearance of any new lesions. Not evaluable (NE) was defined when insufficient data for response evaluation are available.

Before enrolling the patients into the study, the original protocol was approved by the Institutional Review Board (IRB) in each participating institute. The new protocol including the above-mentioned amendment was also approved by IRB in all participating institutes before restarting the study.

RESULTS

Patients' Characteristics

Between December 1998 and December 2000, 28 patients with advanced ovarian cancer were enrolled in this study. One patient was excluded from the study because sufficient laboratory data were not available for analysis. The median age of the 27 eligible patients was 56 years (range, 24–71 years) and 27 patients received 3–6 courses of chemotherapy (mean, 5.4 courses). Additional patients' characteristics are summarized in Table 1.

Dose Escalation and Dose-limiting Toxicity

Excluding one ineligible patient, whose neutrophils were not counted during the first course of chemotherapy, nine patients were enrolled into dose level 1. Among these nine patients, only one developed DLT, grade 4 diarrhea, so the dose escalation was allowed. The following six patients were enrolled into dose level 2. These six patients developed no DLT and further dose escalation was performed. The next six patients enrolled into dose level 3 did not develop DLT and the dose was escalated to level 4. Six subsequent patients were enrolled into dose level 4. Two patients developed DLT; one patient developed febrile neutropenia matching criterion (b) and grade 4 diarrhea and another patient developed prolonged grade 4 neutropenia matching criterion (a). The MTD defined in the protocol had not been reached even at dose level 4. Therefore,