APPENDIX (Cont'd)

Pennsylvania Hospital, Southwest Oncology Group, Washington University School of Medicine, Memorial Sloan-Kettering Cancer Center, Columbus Cancer Council, University of Massachusetts Medical Center, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma Health Science Center, University of Virginia Health Science Center, University of Chicago, University of Arizona Health Science Center, Tacoma General Hospital, Eastern Collaborative Oncology Group, Thomas Jefferson University Hospital, Case Western Reserve University, and Tampa Bay Cancer Consortium.

REFERENCES

1. McGuire WP, Hoskins WJ, Brady MF, et al: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 334:1-6, 1996
2. Piccart MJ, Bertelsen K, James K, et al: Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three-year results. J Natl Cancer Inst 92:699-708, 2000
3. Markman M: Intraperitoneal therapy of ovarian cancer. Semin Oncol 25:356-360, 1998
4. Alberts DS, Liu PY, Hannigan EV, et al: Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 335:1950-1955, 1996
5. Shapiro F, Schneider J, Markman M, et al: High-intensity intravenous cyclophosphamide and cisplatin, interim surgical debulking, and intraperitoneal cisplatin in advanced ovarian carcinoma: A pilot trial with ten-year follow-up. Gynecol Oncol 67:39-45, 1997
6. Calvert AH, Newell DR, Gumbrell LA, et al: Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748-1756, 1989
7. Jelliffe RW: Creatinine clearance: Bedside estimate. Ann Intern Med 79:604-605, 1973
8. Schoenfeld, D: Sample-sizes for the Proportional Hazards Regression Model. Biometrics 39:499-503, 1983
9. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
10. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemo Rep 50:163-170, 1966
11. Cox DR: Regression model and life tables (with discussion). J R Stat Soc Series B 34:187-220, 1972
12. Snedecor GW, Cochran WG: Statistical Methods (ed 6). Ames, IA, The Iowa State University Press, 1967
13. Ozols RF, Locker GY, Doroshow JH, et al: Pharmacokinetics of adriamycin and tissue penetration in murine ovarian cancer. Cancer Res 39:3209-3214, 1979
14. Los G, Mutsaers PHA, van der Vijgh WJF, et al: Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: A comparison with systemic chemotherapy. Cancer Res 49:3380-3384, 1989
15. West GW, Weichselbau R, Little JB: Limited penetration of methotrexate into human osteosarcoma spheroids as a proposed model for solid tumor resistance to adjuvant chemotherapy. Cancer Res 40:3665-3668, 1980
16. Markman M, Reichman B, Hakes T, et al: Responses to second-line cisplatin-based intraperitoneal therapy in ovarian cancer: Influence of a prior response to intravenous cisplatin. J Clin Oncol 9:1801-1805, 1991
17. Markman M, Berek JS, Blessing JA, et al: Characteristics of patients with small-volume residual ovarian cancer unresponsive to cisplatin-based IP chemotherapy: Lessons learned from a Gynecologic Oncology Group phase II trial of IP cisplatin and recombinant alpha-interferon. Gynecol Oncol 45:3-8, 1992
18. Markman M, Blessing JA, Major F, et al: Salvage intraperitoneal therapy of ovarian cancer employing cisplatin and etoposide: A Gynecologic Oncology Group study. Gynecol Oncol 50:191-195, 1993
19. McGuire WP, Hoskins WJ, Brady MF, et al: Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 13:1589-1599, 1995
20. Wrigley E, Weaver A, Jayson G, et al: A randomized trial investigating the dose intensity of primary chemotherapy in patients with ovarian carcinoma: A comparison of chemotherapy given every four weeks with the same chemotherapy given at three week intervals. Ann Oncol 7:705-711, 1996
21. Gore M, Mainwaring P, A'Hern R, et al: Randomized trial of dose-intensity with single-agent carboplatin in patients with epithelial ovarian cancer. J Clin Oncol 16:2426-2434, 1998
22. Kaye SB, Paul J, Cassidy J, et al: Mature results of a randomized trial of two doses of cisplatin for the treatment of ovarian cancer: Scottish Gynecology Cancer Trials Group. J Clin Oncol 14:2113-2119, 1996
23. Markman M, Rowinsky E, Hakes T, et al: Phase I trial of intraperitoneal Taxol: A Gynecologic Oncology Group study. J Clin Oncol 10:1485-1491, 1992
24. Francis P, Rowinsky E, Schneider J, et al: Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: A Gynecologic Oncology Group pilot study. J Clin Oncol 13:2961-2967, 1995
25. Markman M, Brady MF, Spirtos NM, et al: Phase II trial of intraperitoneal paclitaxel in carcinoma of the ovary, tube and peritoneum: A Gynecologic Oncology Group study. J Clin Oncol 16:2620-2624, 1998

文献 5

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

Deborah K. Armstrong, M.D., Brian Bundy, Ph.D., Lari Wenzel, Ph.D., Helen Q. Huang, M.S., Rebecca Baergen, M.D., Shashikant Lele, M.D., Larry J. Copeland, M.D., Joan L. Walker, M.D., and Robert A. Burger, M.D., for the Gynecologic Oncology Group*

From the Johns Hopkins Kimmel Cancer Center, Baltimore (D.K.A.); the Gynecologic Oncology Group Statistical and Data Center (B.B., H.Q.H.) and Gynecologic Oncology (S.L.), Roswell Park Cancer Institute, Buffalo, N.Y.; the University of California, Irvine, Irvine (L.W.); the New York–Presbyterian Hospital, Weill Medical College of Cornell University, New York (R.B.); Ohio State University, Columbus (L.J.C.); the University of Oklahoma, Oklahoma City (J.L.W.); and the Division of Gynecologic Oncology, University of California, Irvine, Orange (R.A.B.). Address reprint requests to Denise Mackey at the Gynecologic Oncology Group, Administrative Office, 4 Penn Ctr., 1600 JFK Blvd., Ste. 1020, Philadelphia, PA 19103, or at dmackey@gog.org.

*The Gynecologic Oncology Group member institutions that participated in this study are listed in the Appendix.

N Engl J Med 2006;354:34-43.

ABSTRACT

BACKGROUND

Standard chemotherapy for newly diagnosed ovarian cancer is a platinum–taxane combination. The Gynecologic Oncology Group conducted a randomized, phase 3 trial that compared intravenous paclitaxel plus cisplatin with intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel in patients with stage III ovarian cancer.

METHODS

We randomly assigned patients with stage III ovarian carcinoma or primary peritoneal carcinoma with no residual mass greater than 1.0 cm to receive 135 mg of intravenous paclitaxel per square meter of body-surface area over a 24-hour period followed by either 75 mg of intravenous cisplatin per square meter on day 2 (intravenous-therapy group) or 100 mg of intraperitoneal cisplatin per square meter on day 2 and 60 mg of intraperitoneal paclitaxel per square meter on day 8 (intraperitoneal-therapy group). Treatment was given every three weeks for six cycles. Quality of life was assessed.

RESULTS

Of 429 patients who underwent randomization, 415 were eligible. Grade 3 and 4 pain, fatigue, and hematologic, gastrointestinal, metabolic, and neurologic toxic effects were more common in the intraperitoneal-therapy group than in the intravenous-therapy group ($P \leq 0.001$). Only 42 percent of the patients in the intraperitoneal-therapy group completed six cycles of the assigned therapy, but the median duration of progression-free survival in the intravenous-therapy and intraperitoneal-therapy groups was 18.3 and 23.8 months, respectively ($P=0.05$ by the log-rank test). The median duration of overall survival in the intravenous-therapy and intraperitoneal-therapy groups was 49.7 and 65.6 months, respectively ($P=0.03$ by the log-rank test). Quality of life was significantly worse in the intraperitoneal-therapy group before cycle 4 and three to six weeks after treatment but not one year after treatment.

CONCLUSIONS

As compared with intravenous paclitaxel plus cisplatin, intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival in patients with optimally debulked stage III ovarian cancer.

OVARIAN CANCER IS THE LEADING CAUSE of death from a gynecologic cancer in the United States.[1] In most cases, the high death rate is due to tumor that has spread beyond the ovary at the time of diagnosis.[2] In the United States, the standard chemotherapy for the initial treatment of ovarian cancer is a combination of a platinum analogue with paclitaxel.[3,4] With modern surgical interventions and contemporary chemotherapy, most patients attain complete clinical remission.[3,5] The majority of them, however, will eventually have a relapse and die of the disease.

The peritoneal cavity is the principal site of disease in ovarian cancer.[2,6] Although the intensity of intravenous chemotherapy is limited mainly by myelotoxicity, several active drugs can be administered directly into the peritoneal cavity. The rationale for intraperitoneal therapy in ovarian cancer is that the peritoneum, the predominant site of tumor, receives sustained exposure to high concentrations of antitumor agents while normal tissues, such as the bone marrow, are relatively spared.

Two randomized, phase 3 intergroup trials have compared intraperitoneal with intravenous chemotherapy in advanced, low-volume ovarian cancer.[7,8] The first demonstrated a statistically significant survival advantage among patients treated with intraperitoneal chemotherapy, but the regimen did not include paclitaxel.[7] The second trial showed a significant difference in progression-free survival, but the difference in overall survival was of borderline significance (P=0.05). Furthermore, the intraperitoneal-therapy group included two cycles of moderately intensive intravenous carboplatin, which complicated the interpretation of results and added to the toxicity of the treatment.[8] Neither of these trials led to widespread acceptance of intraperitoneal treatment. The reluctance of clinicians to embrace intraperitoneal therapy is due to multiple factors, including its high cost and toxicity and clinicians' lack of familiarity with peritoneal administration and catheter-placement techniques. The possibility that improved outcomes with newer forms of therapy could replace intraperitoneal treatment has also been a consideration.[9,10]

We report the results of a randomized, phase 3 trial in which a regimen of six cycles of treatment with intravenous paclitaxel followed by intravenous cisplatin was compared with six cycles of intravenous paclitaxel followed by intraperitoneal cisplatin and intraperitoneal paclitaxel in women with previously untreated stage III ovarian cancer.

METHODS

PATIENTS

Eligible patients had stage III epithelial ovarian or peritoneal carcinoma with no residual mass greater than 1.0 cm in diameter after surgery, a Gynecologic Oncology Group (GOG) performance status of 0 to 2 (with 0 being fully active and 4 completely disabled), normal blood counts, and adequate renal and hepatic function. All cases were centrally reviewed by the GOG to confirm patients' surgical and pathological eligibility for enrollment. This review was not strictly blinded. However, pathology reports, operative notes, and eligibility information were collected before registration. Patients who had undergone prior chemotherapy or radiation for ovarian cancer were not eligible. All patients gave written informed consent according to institutional and federal guidelines before enrollment. Approval was granted by the institutional review board at each participating site.

At registration, participants decided whether they would undergo a second-look laparotomy at the completion of chemotherapy. At study entry and before each treatment, a physical examination was performed and medical history taking, complete blood count, blood chemical measurements, and measurement of serum ovarian cancer antigen 125 were carried out. This evaluation was repeated at the completion of therapy, every 3 months for 24 months, and then every 6 months. Quality-of-life assessment, with use of the Functional Assessment of Cancer Therapy — Ovarian (FACT-O) instrument,[11] was performed four times: at registration, before cycle 4, 3 to 6 weeks after cycle 6, and 12 months after the completion of therapy. All patients were followed for clinical progression and death.

TREATMENT PLAN

Patients were randomly assigned to receive either 135 mg of intravenous paclitaxel per square meter of body-surface area over a 24-hour period on day 1 followed by 75 mg of intravenous cisplatin per square meter on day 2 (intravenous-therapy group) or 135 mg of intravenous paclitaxel per square meter over a 24-hour period on day 1 followed by 100 mg of intraperitoneal cisplatin per

square meter on day 2 and 60 mg of intraperitoneal paclitaxel per square meter on day 8 (intraperitoneal-therapy group). Standard premedication was given to prevent hypersensitivity reactions to paclitaxel. Hydration and antiemetic agents were given before cisplatin was administered. For intraperitoneal therapy, paclitaxel or cisplatin was reconstituted in 2 liters of warmed normal saline and infused as rapidly as possible through an implantable peritoneal catheter. Treatments were administered every three weeks for six cycles.

Before they could receive a subsequent cycle of therapy, patients were required to have an absolute neutrophil count of 1500 cells per cubic millimeter or greater, a platelet count of 100,000 cells per cubic millimeter or greater, and a creatinine level of 2.0 mg per deciliter or less. Treatment modifications for hematologic toxic effects included cycle delay, dose reduction, and the addition of granulocyte colony-stimulating factor (in that sequence). There was no dose modification if the nadir of leukopenia was not accompanied by fever. Treatment was postponed in the case of grade 3 or 4 peripheral neuropathy, a creatinine level greater than 2.0 mg per deciliter, or a creatinine clearance of less than 50 ml per minute. Patients in whom treatment was delayed for more than three weeks were removed from the study.

Among patients in the intraperitoneal-therapy group, the dose of intraperitoneal drug was reduced if there was grade 2 abdominal pain. Patients with grade 3 abdominal pain, recurrent grade 2 abdominal pain after a dose reduction, or complications involving the intraperitoneal catheter that prohibited further intraperitoneal therapy received intravenous chemotherapy for the remaining cycles. The dose of cisplatin was reduced if there was grade 2 peripheral neuropathy. Women in either group who had a cisplatin-related toxic effect requiring discontinuation of the protocol treatment received intravenous therapy, with carboplatin substituted for cisplatin.

If second-look assessment was elected at registration, it was performed within 8 weeks after the last cycle of chemotherapy and no later than 29 weeks after study entry. Categories of pathological response were defined as follows: negative (i.e., there was a complete response), positive with microscopic disease only, or positive with grossly visible persistent disease.

STATISTICAL ANALYSIS

The GOG Statistical and Data Center randomly assigned patients to one of the two treatment groups, with stratification according to residual disease (grossly visible disease vs. no visible disease) and the second-look surgery option (selected vs. declined), with use of a permuted block containing three assignments for each regimen. A sample size of 384 eligible patients was set, with sufficient follow-up to observe 208 recurrences (and 208 deaths) before final testing of the primary hypothesis, which was based on the following research question: Does the use of intraperitoneal cisplatin and paclitaxel improve progression-free and overall survival as compared with intravenous cisplatin and paclitaxel? This sample size provided 90 percent statistical power with the use of a one-sided log-rank test,[12] an alpha level of 0.05, and a hazard ratio (for intravenous vs. intraperitoneal administration) of 1.5.[13] Projections indicated that 61 percent of the patients in the intravenous-therapy group would have died by the time of the final analysis.

The primary study end points — progression-free survival and overall survival — were measured from the date of randomization. Survival was measured up to the date of death or, for living patients, the date of last contact. The duration of progression-free survival was the time until progression, death, or the date of last contact, whichever came first. The planned analyses of overall survival and progression-free survival included only eligible patients (on the basis of the intention-to-treat principle). All causes of death were used in the calculation of overall survival. Estimates of the cumulative proportions of survival were based on the Kaplan–Meier procedure.[14] Estimates of the relative risk and confidence intervals for treatment effects with respect to progression and death were generated with use of the Cox model.[15] Primary unadjusted estimates were calculated with use of the two stratification factors as covariates. Adjusted estimates were based on two previously identified additional covariates (age and histologic features).[16]

Eligible women who received at least one cycle of treatment were assessed for toxic effects. Patients in the intraperitoneal-therapy group who had complications related to the intraperitoneal catheter were assessed for toxic effects, regardless

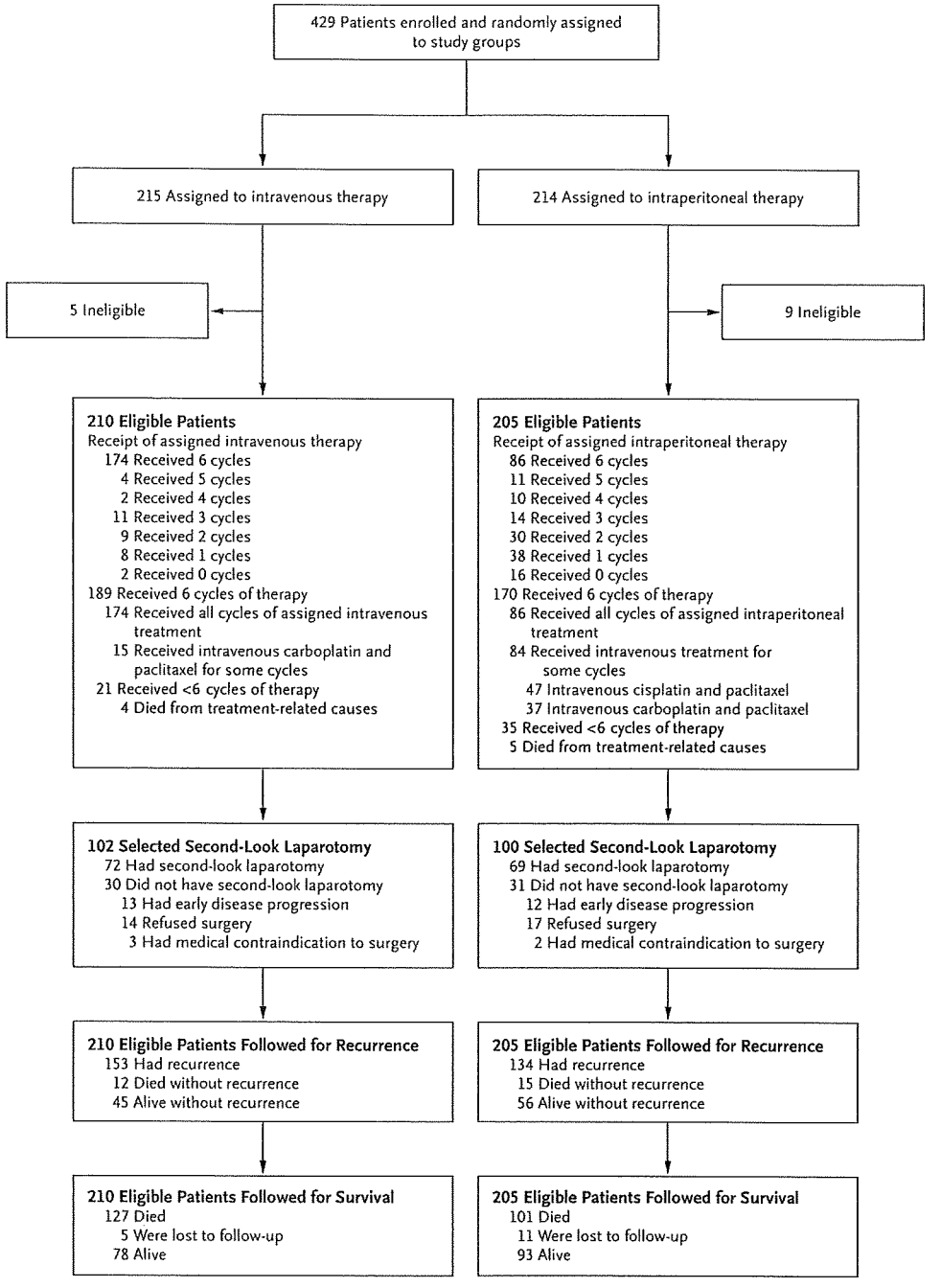

Figure 1. Study Patients.

Table 1. Characteristics of the Patients.*

Characteristic	Intravenous-Therapy Group (N=210)	Intraperitoneal-Therapy Group (N=205)
	no. (%)	
Second-look laparotomy		
Not elected	108 (51)	105 (51)
Elected	102 (49)	100 (49)
Age at diagnosis		
21–30 yr	0	4 (2)
31–40 yr	15 (7)	8 (4)
41–50 yr	43 (20)	52 (25)
51–60 yr	74 (35)	62 (30)
61–70 yr	56 (27)	53 (26)
71–80 yr	19 (9)	24 (12)
>80 yr	3 (1)	2 (1)
Race or ethnic group†		
Hispanic	9 (4)	9 (4)
Asian or Pacific Islander	9 (4)	4 (2)
Black	4 (2)	7 (3)
White	187 (89)	185 (90)
Other	1 (<1)	0
GOG performance status		
0	90 (43)	91 (44)
1	112 (53)	99 (48)
2	8 (4)	15 (7)
Histologic type		
Serous adenocarcinoma	170 (81)	158 (77)
Endometrioid adenocarcinoma	12 (6)	17 (8)
Mixed epithelial carcinoma	11 (5)	14 (7)
Clear-cell carcinoma	9 (4)	11 (5)
Other type	8 (4)	5 (2)
Histologic grade‡		
1	18 (9)	25 (12)
2	83 (40)	72 (35)
3	106 (50)	106 (52)
Gross residual disease		
No	75 (36)	78 (38)
Yes	135 (64)	127 (62)
Disease		
Ovarian cancer	183 (87)	184 (90)
Primary peritoneal cancer	27 (13)	21 (10)

* Because of rounding, not all percentages total 100.
† Race or ethnic group was determined by the investigator or was self-reported at each site.
‡ Five cases were not graded.

of their ability to receive treatment. The Wilcoxon rank-sum test was used to test the independence of the risk of severe and life-threatening toxic effects (grade 0, 1, or 2 vs. grade 3 vs. grade 4) from the assigned treatment.[17]

Quality-of-life assessments from baseline to follow-up (conducted before the fourth cycle, 3 to 6 weeks after the sixth cycle, and 12 months after the sixth cycle) were analyzed with linear models with an unstructured covariance matrix. Patients' age, performance status at randomization, and baseline assessment scores were potential covariates. The restricted maximum likelihood was used to estimate the covariance parameters. Quality of life was a secondary end point. All P values are two-sided.

RESULTS

PATIENTS

Between March 1998 and January 2001, 429 women were randomly assigned to the intravenous-therapy group (215 patients) or the intraperitoneal-therapy group (214 patients) (Fig. 1). Fourteen patients were ineligible (five in the intravenous-therapy group and nine in the intraperitoneal-therapy group) for the following reasons: stage other than optimal stage III (three patients), the presence of a second primary cancer (one patient), a nonepithelial cell type (five patients), a primary cancer other than ovarian or peritoneal carcinoma (one patient), inadequate surgery (two patients), or a tumor with low malignant potential (two patients). Table 1 shows the characteristics of the 415 eligible patients whose data form the basis of this report.

TOXICITY

Of the 210 eligible patients assigned to the intravenous-therapy group, 189 (90 percent) completed six cycles of chemotherapy, and 174 (83 percent) received all six cycles of the assigned intravenous therapy (Fig. 1). Of the 205 eligible patients assigned to the intraperitoneal-therapy group, 170 (83 percent) completed six cycles of chemotherapy, and 86 (42 percent) received all six cycles of the assigned intraperitoneal therapy. For patients in either group who had intolerable toxic effects related to cisplatin, that drug was switched to intravenous carboplatin. The primary reason for discontinuation of intraperitoneal therapy was catheter-related complications.[18] There were

nine treatment-related deaths, four in the intravenous-therapy group and five in the intraperitoneal-therapy group. All nine treatment-related deaths were attributed to infection. Of the five treatment-related deaths in the intraperitoneal-therapy group, three were also partially attributed to the tumor.

Table 2 lists adverse events. Significantly more patients in the intraperitoneal-therapy group than in the intravenous-therapy group had severe or life-threatening (grade 3 or 4) fatigue, pain, or hematologic, gastrointestinal, metabolic, or neurologic toxic effects (P≤0.001).

Table 2. Frequency of Grade 3 or 4 Adverse Events.

Adverse Event	Intravenous-Therapy Group (N=210)	Intraperitoneal-Therapy Group (N=201)*	P Value†
	no. (%)		
Leukopenia‡	134 (64)	152 (76)	<0.001
Platelet count <25,000/mm³	8 (4)	24 (12)	0.002
Other hematologic event	190 (90)	188 (94)	0.87
Gastrointestinal event	51 (24)	92 (46)	<0.001
Renal or genitourinary event	5 (2)	14 (7)	0.03
Pulmonary event	5 (2)	7 (3)	0.50
Cardiovascular event	10 (5)	19 (9)	0.06
Neurologic event	18 (9)	39 (19)	0.001
Cutaneous change	2 (1)	2 (1)	0.96
Event involving lymphatic system	0	3 (1)	0.07
Fever	8 (4)	19 (9)	0.02
Infection	12 (6)	33 (16)	0.001
Fatigue	9 (4)	36 (18)	<0.001
Metabolic event	15 (7)	55 (27)	<0.001
Pain	3 (1)	23 (11)	<0.001
Hepatic event	1 (<1)	6 (3)	0.05
Other	1 (<1)	6 (3)	0.05

* Four patients did not receive any protocol-based therapy.
† P values were calculated by the Wilcoxon rank-sum test (grades 0, 1, and 2 vs. grades 3 and 4).
‡ A white-cell count below 1000 per cubic millimeter was considered to indicate leukopenia.

PATHOLOGICAL RESPONSES AT SECOND-LOOK LAPAROTOMY

Second-look laparotomy after the completion of therapy was not mandatory, and the results of second-look surgery were not an end point of this study. Of the 415 eligible patients, 202 (49 percent) registered for second-look surgery. The frequency of refusal and the rate of medical contraindication to the procedure were similar in the two groups. The rate of complete pathological response was 41 percent in the intravenous group (35 of 85 patients had such a response) and 57 percent in the intraperitoneal group (46 of 81 patients).

SURVIVAL

The median duration of follow-up was 48.2 months in the intravenous-therapy group and 52.6 months in the intraperitoneal-therapy group, with 5 and 11 patients, respectively, lost-to-follow-up. The median progression-free survival was 18.3 months in the intravenous-therapy group and 23.8 months in the intraperitoneal-therapy group (Fig. 2A and Table 3). The median overall survival was 49.7 and 65.6 months, respectively (Fig. 2B and Table 3). Table 3 lists relative risks, 95 percent confidence intervals, and P values for progression-free and overall survival in the two groups. The adjusted estimates of the relative risk of recurrence and death (0.77 and 0.73, respectively, in the intraperitoneal-therapy group as compared with the intravenous-therapy group) were similar to the primary estimates (0.80 and 0.75, respectively). There was no statistical difference in the risk reduction associated with intraperitoneal therapy between the subgroup with gross visible residual disease and the subgroup with no visible residual disease at initial surgery (Table 3). An analysis that included all randomly assigned patients (eligible and ineligible) yielded negligible changes in the relative-risk estimates.

Before randomization, patients in the intraperitoneal-therapy group reported lower FACT-O (quality-of-life) scores than those in the intravenous group. After adjustments were made for age, performance status, and the baseline FACT-O score, patients receiving intraperitoneal therapy reported worse quality of life before cycle 4 (P<0.001) and three to six weeks after treatment (P=0.009). There were no significant quality-of-life differences between the groups one year after treatment (Table 4). Differences in neurotoxic effects and abdominal discomfort between the two groups have been reported elsewhere.[19,20]

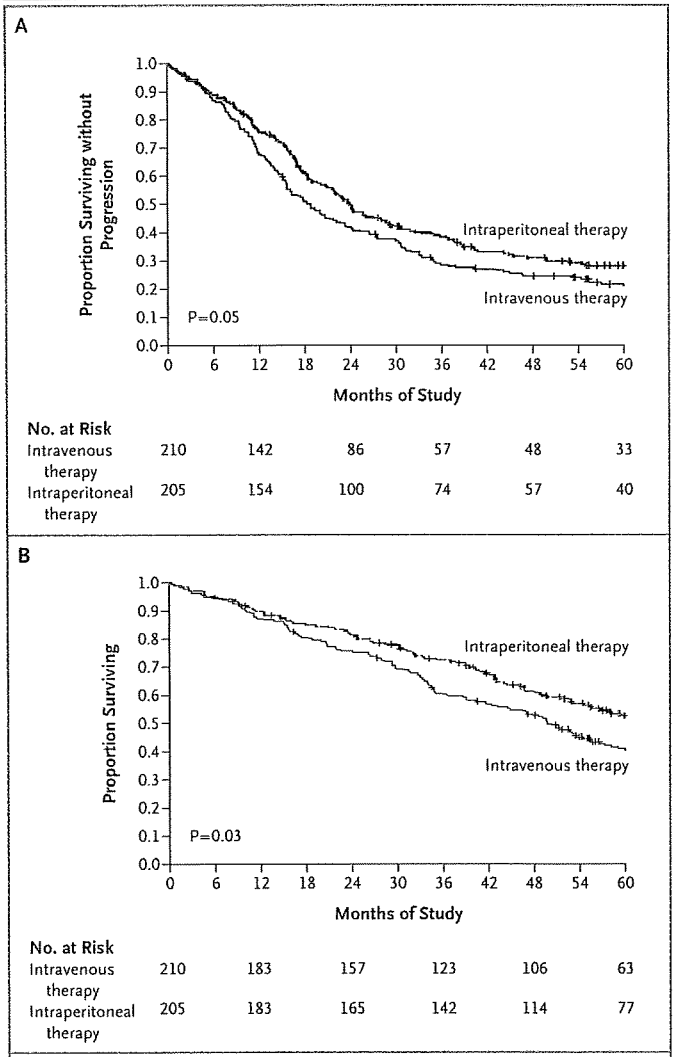

Figure 2. **Progression-free and Overall Survival.**

Panel A shows progression-free survival and Panel B overall survival among the 415 eligible patients with stage III ovarian cancer who were randomly assigned to treatment with intravenous paclitaxel and cisplatin or to treatment with intravenous paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel. Eighty-five percent of the patients either died or were followed for five years. As shown in Panel A, treatment failed in 165 patients in the intravenous-therapy group: 153 (73 percent) had a recurrence, and 12 died without a documented recurrence. Forty-five patients in the intravenous-therapy group had no evidence of disease. Treatment failed in 149 patients in the intraperitoneal-therapy group: 134 (65 percent) had a recurrence, and 15 died without a documented recurrence. Fifty-six patients in the intraperitoneal group had no evidence of disease. As shown in Panel B, in the intravenous-therapy group, 127 patients (60 percent) died and 5 were lost to follow-up. Seventy-eight patients in the intravenous-therapy group were alive. In the intraperitoneal-therapy group, 101 patients (49 percent) died and 11 were lost to follow-up. Ninety-three patients in the intraperitoneal-therapy group were alive.

DISCUSSION

An intensive regimen of intravenous paclitaxel followed by intraperitoneal cisplatin and paclitaxel significantly improved progression-free survival (P=0.05) and overall survival (P=0.03) among women with newly diagnosed, optimally debulked stage III ovarian cancer. As compared with the intravenous-therapy group, women who received intraperitoneal treatment had a 25 percent reduction in the risk of death. Among all randomized phase 3 trials conducted by the GOG among patients with advanced ovarian cancer, the current trial yielded the longest median survival: 65.6 months, in the group of patients who received intraperitoneal therapy.

Ovarian cancer commonly spreads within the peritoneal cavity; there is a reduced likelihood of substantial hematogenous or lymphatic dissemination. Successful tumor cytoreduction with modern surgical approaches allows chemotherapy to be administered in the setting of low-volume residual disease within the peritoneal cavity. The rationale for intraperitoneal administration is supported by preclinical and pharmacokinetic data and, with this study, a growing body of clinical data. In a previous GOG study, doubling the dose of intravenous cisplatin and cyclophosphamide did not improve survival.[21] Furthermore, the strategy of increasing the dose density or dose intensity of systemic platinum agents is limited by the nonhematologic toxicity of cisplatin and the lack of a reliable platelet growth factor to overcome carboplatin-related thrombocytopenia. These limitations can be overcome, in part, by intraperitoneal administration.

Patients in the intraperitoneal-therapy group had more toxic events than women in the intravenous-therapy group. These toxic events may be attributed to the higher dose of cisplatin in the intraperitoneal-therapy group. The rationale for increasing the cisplatin dose is that capillary uptake of cisplatin from peritoneal surfaces is slow and incomplete, resulting in systemic exposure that is prolonged but lower than that with intravenous administration.[22] The dose of intraperitoneal cisplatin used in this study has previously been given in combination with intravenous paclitaxel[8] and with intravenous cyclophosphamide[7] and in a phase 2 trial of the same regimen[23] with acceptable toxicity. Alternatively, the increased incidence of toxic events

Table 3. Summary of Comparisons between the Treatment Groups.

Variable	Median Duration		No. of Events*		Relative Risk (95% CI)†	P Value
	Intravenous-Therapy Group	Intraperitoneal-Therapy Group	Intravenous-Therapy Group	Intraperitoneal-Therapy Group		
	mo					
Progression-free survival	18.3	23.8	165	149	0.80 (0.64–1.00)	0.05
Gross residual disease	15.4	18.3	115	105	0.81 (0.62–1.05)	0.97‡
No visible residual disease	35.2	37.6	50	44	0.80 (0.54–1.21)	
Overall survival	49.7	65.6	127	101	0.75 (0.58–0.97)	0.03
Gross residual disease	39.1	52.6	95	77	0.77 (0.57–1.04)	0.72‡
No visible residual disease	78.2	NA§	32	24	0.69 (0.41–1.17)	

* Events were a recurrence of disease or death without documented recurrence in the analysis of progression-free survival and death regardless of cause in the analysis of overall survival.
† The relative risk is the risk of recurrence or death in the intraperitoneal-therapy group as compared with that in the intravenous-therapy group. The primary estimate for the entire study group included the covariates of residual-disease status and the second-look surgery option.
‡ The P value was calculated by a test for the homogeneity of relative risk between the two categories of residual-disease status.
§ NA denotes not applicable because the medians for survival had not yet been reached.

in the intraperitoneal-therapy group may be due to the intraperitoneal paclitaxel. Paclitaxel persists in the peritoneum for one week after intraperitoneal administration, suggesting that peritoneal clearance is very slow.[24] Nevertheless, with the dose used in this study, paclitaxel is detectable in the plasma after intraperitoneal administration.[24] It is possible that peritoneal clearance of paclitaxel is altered when the drug is given after intraperitoneal cisplatin, as it was in this study, or that even low blood levels of paclitaxel one week after the administration of intravenous paclitaxel and intra-peritoneal cisplatin can increase toxicity. Careful monitoring of toxicity and the use of contemporary supportive care measures might improve the tolerability of the regimen we used. However, it is not known whether altering the intraperitoneal regimen to decrease toxicity will affect its efficacy.

Given the increased toxicity associated with intraperitoneal therapy, an important secondary outcome of this study was the quality of life. Patients in the intraperitoneal-therapy group reported worse quality of life before cycle 4 and three to six weeks after treatment was completed than did those in the intravenous-therapy group. These differences were not observed one year after treatment was completed, at which time quality-of-life scores had improved relative to baseline in both groups.

A substantial portion of patients in the intraperitoneal-therapy group had toxic effects and treatment intolerance related to the catheter required for intraperitoneal administration. In this group, 48 percent received three or fewer cycles of intraperitoneal treatment, and only 42 percent received all six assigned cycles of intraperitoneal therapy. The type of catheter and the timing of catheter placement were not specified in the study design. A separate, detailed evaluation of intraperitoneal catheter–related outcomes in this study showed that patients who had a left colonic or rectosigmoid resection at the time of initial surgery were less likely to receive all planned doses of intraperitoneal therapy.[18] The single-lumen venous-access catheter attached to an implanted subcutaneous port has been reported to be superior to the fenestrated catheter designed for intraperitoneal use, with minimal fibrous-sheath formation and a markedly reduced risk of small-bowel obstruction or perforation.[25] Thus, standardization of the device to be used and the technique and timing of port implantation could improve the success of intraperitoneal therapy.

Although fewer than half the patients assigned to the intraperitoneal group received six cycles of intraperitoneal treatment, the group as a whole had a significant improvement in survival as compared with the intravenous group. It is possible that most of the benefit of intraperitoneal therapy occurs early, during the initial cycles, or that

Table 4. Mean FACT-O Quality-of-Life Scores in the Two Groups at Each Assessment Point.*

Assessment Point	Intravenous-Therapy Group		Intraperitoneal-Therapy Group		Mean Difference (95% CI)†	P Value
	No. of Patients	Score	No. of Patients	Score		
Before randomization	201	111.9±19.3	198	106.4±20.5	5.0 (1.2 to 8.8)	0.03‡
Before fourth cycle	172	114.7±18.6	148	103.3±19.2	8.9 (5.3 to 12.5)	<0.001§
3–6 Wk after sixth cycle	171	118.4±19.2	159	110.5±21.0	5.2 (1.3 to 9.1)	0.009§
12 Mo after sixth cycle	140	127.2±19.1	139	125.5±19.2	1.2 (−5.1 to 2.8)	0.56§

* Plus–minus values are means ±SD. Lower Functional Assessment of Cancer Therapy — Ovarian (FACT-O) scores (ranging from 0 to 156) indicate poorer quality of life. CI denotes confidence interval.
† The mean difference is the estimated adjusted mean value in the intravenous-therapy group minus the corresponding mean value in the intraperitoneal-therapy group.
‡ The P value was calculated with use of the general linear model, with adjustment for age and performance status at randomization.
§ The P value was calculated with use of the linear mixed model, with adjustment for age, performance status, and baseline FACT-O score.

the benefit of intraperitoneal therapy may be greater if more patients can successfully complete six cycles of treatment. This study was not designed to address the effect of the duration of treatment on clinical outcome, and retrospective analysis of this variable has the potential for bias. Possible means of improving the tolerability of intraperitoneal treatment include identification and exclusion of patients at risk for poor tolerance, modification of the dose of drug used, alteration of the administration schedule, and use of less toxic chemotherapeutic agents. Studies of intraperitoneal carboplatin,[26] of weekly intraperitoneal paclitaxel, and of combinations of intravenous paclitaxel and intraperitoneal docetaxel may identify regimens with improved tolerance. Since modifications that improve tolerability may decrease antitumor efficacy, these approaches will require rigorous testing in randomized trials before they can be recommended.

Including this study, there are now three randomized trials showing that intraperitoneal chemotherapy has a clinical advantage in the treatment of ovarian cancer. Although this advantage comes at the expense of increased toxicity and reduced quality of life during treatment, these results should encourage the use of intraperitoneal chemotherapy in patients with advanced ovarian cancer.

Supported by grants (CA 27469, to the Gynecologic Oncology Group Administrative Office, and CA 37517, to the Gynecologic Oncology Group Statistical and Data Center) from the National Cancer Institute.

No potential conflict of interest relevant to this article was reported.

We are indebted to Anne Reardon for assistance in the preparation of the manuscript.

APPENDIX

The following Gynecologic Oncology Group member institutions participated in this study: the University of Alabama at Birmingham, Duke University Medical Center, Abington Memorial Hospital, Walter Reed Army Medical Center, Wayne State University, the University of Minnesota Medical School, the University of Mississippi Medical Center, the Colorado Foundation for Medical Care, the University of California Medical Center at Los Angeles, the University of Washington Medical Center, the Hospital of the University of Pennsylvania, the Milton S. Hershey School of Medicine of the Pennsylvania State University, the University of Cincinnati College of Medicine, the University of North Carolina School of Medicine, the University of Iowa Hospitals and Clinics, the University of Texas Southwestern Medical Center at Dallas, Indiana University School of Medicine, Wake Forest University School of Medicine, the University of California, Irvine, Medical Center, Tufts New England Medical Center, Rush–Presbyterian-St. Luke's Medical Center, the University of Kentucky, National Cancer Institute–Community Clinical Oncology Program, the Cleveland Clinic Foundation, State University of New York at Stony Brook, Washington University School of Medicine, Columbus Cancer Council, the University of Massachusetts Medical Center, the Women's Cancer Center of California, University of Oklahoma, the University of Virginia, the University of Chicago, Tacoma General Hospital, Thomas Jefferson University Hospital, the Mayo Clinic, Case Western Reserve University, Tampa Bay Cancer Consortium, North Shore University Hospital, Brookview Research, and Ellis Fischel Cancer Center.

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005; 55:10-30. [Erratum, CA Cancer J Clin 2005; 55:259.]
2. Cannistra SA. Cancer of the ovary. N Engl J Med 2004;351:2519-29.
3. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1-6.
4. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003;21:3194-200.
5. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002; 20:1248-59.
6. Thigpen T. The if and when of surgical debulking for ovarian carcinoma. N Engl J Med 2004;351:2544-6.
7. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 1996;335:1950-5.
8. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:1001-7.
9. McGuire WP. Intraperitoneal therapy for ovarian cancer: a sacrifice bunt. J Clin Oncol 2001;19:921-3.
10. Ozols RF, Gore M, Trope C, Grenman S. Intraperitoneal treatment and dose-intense therapy in ovarian cancer. Ann Oncol 1999; 10:Suppl 1:59-64.
11. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, et al. Reliability and validity of the Functional Assessment of Cancer Therapy — Ovarian. J Clin Oncol 2001; 19:1809-17.
12. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163-70.
13. Schoenfeld D. Sample-size formula for the proportional-hazards regression model. Biometrics 1983;39:499-503.
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
15. Cox DR. Regression models and life tables. J R Stat Soc [B] 1972;34:187-220.
16. Greer BE, Bundy BN, Ozols RF, et al. Implications of second-look laparotomy in the context of optimally resected stage III ovarian cancer: a non-randomized comparison using an explanatory analysis: a Gynecologic Oncology Group study. Gynecol Oncol 2005;99:71-9.
17. Hollander M, Wolfe DA. Nonparametric statistical methods. 2nd ed. New York: John Wiley, 1999.
18. Walker JL, Armstrong DK, Huang HQ, et al. Intraperitoneal catheter outcomes in a phase 3 trial of intravenous vs. intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2006;100:27-32.
19. Wenzel LB, Huang H, Armstrong D, Walker J, Cella D. Quality of life (QOL) results of a randomized study of intravenous (IV) paclitaxel and cisplatin vs intravenous paclitaxel, intraperitoneal (intraperitonal) cisplatin and intraperitonal paclitaxel in optimal stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group trial. Proc Am Soc Clin Oncol 2004;23:454. abstract.
20. *Idem.* Validation of a FACT/GOG-Abdominal Discomfort (AD) subscale: a Gynecologic Oncology Group (GOG) study. Proc Am Soc Clin Oncol 2005;23:754. abstract.
21. McGuire WP, Hoskins WJ, Brady MF, et al. Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 1995;13:1589-99.
22. Schneider JG. Intraperitoneal chemotherapy. Obstet Gynecol Clin North Am 1994;21:195-212.
23. Rothenberg ML, Liu PY, Braly PS, et al. Combined intraperitoneal and intravenous chemotherapy for women with optimally debulked ovarian cancer: results from an intergroup phase II trial. J Clin Oncol 2003;21:1313-9.
24. Francis P, Rowinsky E, Schneider J, Hakes T, Hoskins W, Markman M. Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a Gynecologic Oncology Group pilot study. J Clin Oncol 1995;13:2961-7.
25. Alberts DS, Markman M, Armstrong D, Rothenberg ML, Muggia F, Howell SB. Intraperitoneal therapy for stage III ovarian cancer: a therapy whose time has come! J Clin Oncol 2002;20:3944-46.
26. Fujiwara K, Sakuragi N, Suzuki S, et al. First-line intraperitoneal carboplatin-based chemotherapy for 165 patients with epithelial ovarian carcinoma: results of long-term follow-up. Gynecol Oncol 2003;90: 637-43. [Erratum, Gynecol Oncol 2003;91: 662.]

文献 6

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Gynecologic Oncology 99 (2005) 591 – 596

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Intraperitoneal carboplatin infusion may be a pharmacologically more reasonable route than intravenous administration as a systemic chemotherapy. A comparative pharmacokinetic analysis of platinum using a new mathematical model after intraperitoneal vs. intravenous infusion of carboplatin—A Sankai Gynecology Study Group (SGSG) study

Yasunari Miyagi[a], Keiichi Fujiwara[b,*], Junzo Kigawa[c], Hiroaki Itamochi[c], Shoji Nagao[b], Eriko Aotani[d], Naoki Terakawa[c], Ichiro Kohno[b]

[a]*Okayama Red Cross General Hospital, Okayama City, Japan*
[b]*Department of Obstetrics and Gynecology, Kawasaki Medical School, 577 Kurashiki City, 701-0192, Japan*
[c]*Tottori University, Yonago City, Japan*
[d]*The Kitasato Institute, Tokyo, Japan*

Received 8 April 2005
Available online 10 August 2005

Abstract

Objective. To clarify the pharmacological advantage of carboplatin-based intraperitoneal chemotherapy using the three-compartment mathematical model.

Methods. Eleven consecutive patients in one institution underwent intraperitoneal administration of carboplatin, and 11 consecutive patients in another institution received intravenous administration. Carboplatin (AUC = 6 mg × min/ml) was diluted in 500 ml 5% glucose and administered either as an intraperitoneal bolus infusion or intravenous drip infusion during 1 h. Patients undergoing intravenous injection also received an infusion of 500 ml 5% glucose to obtain intraperitoneal samples. Intraperitoneal fluid and blood samples were obtained, immediately and 1, 2, 4, 8, 12, and 24 h after administration. The mathematical model consisting of a three-compartment model was applied to analyze the pharmacokinetics. The model was created with simultaneous differential equations and was solved by the Runge–Kutta method.

Results. The rate constants of platinum diffusion from the peritoneal cavity to serum, serum to peritoneal cavity, serum to peripheral space, peripheral space to serum, and elimination were 0.94 ± 0.79 (mean ± SD), 1.28 ± 2.50, 16.50 ± 9.26, 0.99 ± 0.62, and 4.14 ± 1.45 (h^{-1}), respectively. When the theoretical pharmacological concentration of platinum was calculated using this mathematical model, 24-h platinum AUC in the serum was exactly the same regardless of intraperitoneal or intravenous administration of carboplatin. However, the 24-h platinum AUC in the peritoneal cavity was approximately 17 times higher when carboplatin was administered by the intraperitoneal route.

Conclusion. The present pharmacological analysis suggests that intraperitoneal infusion of carboplatin is feasible not only as an intraperitoneal regional therapy but also as a more reasonable route for systemic chemotherapy.

Keywords: Intraperitoneal chemotherapy; Intravenous chemotherapy; Carboplatin; Pharmacokinetics; Mathematical model; Ovarian cancer

Introduction

The most characteristic feature of ovarian cancer is an intraperitoneal spread of the disease in its early stages. Therefore, intraperitoneal chemotherapy appears to be a reasonable therapeutical approach, and it has been

* Corresponding author. Fax: +81 86 462 1199.
E-mail address: fujiwara@med.kawasaki-m.ac.jp (K. Fujiwara).

0090-8258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2005.06.055

investigated for many years. Recently, three large randomized trials have shown survival advantages of intraperitoneal over intravenous cisplatin-based chemotherapy in epithelial ovarian cancer patients [1–3]. Despite this survival benefit of intraperitoneal chemotherapy, intraperitoneal cisplatin-based chemotherapy has not become a standard therapy, mainly because of excessive toxicities of the intraperitoneal arm in two of the abovementioned three randomized trials. Recently, the less toxic platinum agent, carboplatin, became a standard platinum compound for epithelial ovarian cancer with equivalent efficacy to that of cisplatin for intravenous administration [4,5]. However, the experience with intraperitoneal carboplatin therapy is limited. We recently reported an excellent survival of ovarian cancer patients who underwent first-line intraperitoneal carboplatin-based chemotherapy with 400 mg/m^2 or more carboplatin [6]. As shown by the results of this retrospective analysis, carboplatin is now becoming an agent of great interest for intraperitoneal chemotherapy. The Gynecologic Oncology Group started a phase I trial of intraperitoneal carboplatin in combination with intravenous paclitaxel.

The pharmacological advantage of intraperitoneal chemotherapy is an exposure of the intraperitoneal disease to extremely high concentrations of anticancer drug while minimizing systemic toxicity. Therefore, a number of drugs have been investigated in order to measure their peritoneum/plasma ratios at peak concentrations and/or the area under the curve (AUC), when these agents were administered into the peritoneal cavity [7,8]. However, a pharmacological study has not been performed to measure the drug concentration in the peritoneal cavity after intravenous administration of anticancer drugs.

We felt it was important to measure the pharmacological parameters to further evaluate the true advantage of intraperitoneal carboplatin administration. In this study, we compare the pharmacokinetics of platinum in the intraperitoneal and intravenous spaces after intraperitoneal or intravenous administration of carboplatin. We also created an original theoretical three-compartment mathematical model, and we evaluated the feasibility of this model by using these pharmacological data.

Patients and methods

Patients

Patients eligible for this study were those with epithelial ovarian cancer who underwent laparotomy for staging or debulking purposes. At the conclusion of the operation, either an implantable port system or a #6 nutrition silicon tube was placed. In order to minimize the possible selection bias, all patients in Tottori University received intravenous carboplatin administration and all patients in Kawasaki Medical School received intraperitoneal carboplatin infusion. All patients must be confirmed to be free of obvious ascites, detectable by abdominal ultrasonogram, when the first chemotherapy was administered after surgery. The patients must not have received prior chemotherapy or abdominopelvic radiation therapy. This study was approved by the institutional ethical review committees and written informed consent was obtained from each patient.

The mean ages of patients in the intraperitoneal and intravenous groups were 55 ± 12 years and 55 ± 10 years, respectively. The mean heights of patients in the intraperitoneal and intravenous groups were 152 ± 5.6 cm and 153 ± 7.5 cm, respectively, and the body weights were 49 ± 7 kg and 51 ± 11 kg, respectively. The performance status of the patients must be 0 to 2; there was no difference between the intraperitoneal and intravenous groups. The distribution of clinical stages was not different between patients who received intraperitoneal or intravenous administration of carboplatin. Therefore, the patient characteristics did not differ between the two groups.

Chemotherapy

All patients underwent intravenous administration of paclitaxel, immediately followed by intravenous or intraperitoneal carboplatin infusion. The dose of paclitaxel was 175 mg/m^2. Paclitaxel was dissolved in 500 ml of 5% dextrose and administered over 3 h. The dose of carboplatin was at an AUC of 6, calculated by the Calvert formula [9]. The glomerular filtration rate was substituted by creatinine clearance in the calculation using the Cockcroft–Gault formula [10]. For intravenous infusion, carboplatin was diluted in 500 ml 5% dextrose and administered over 1 h. For intraperitoneal infusion, 500 ml dextrose was infused through an intraperitoneal catheter, and then the designated dose of carboplatin solution was infused as a bolus.

Carboplatin is most commonly given as a 30-min intravenous infusion in the US. In this study, the pharmacokinetics of intravenous carboplatin were studied using 1-h infusion, because 1-h intravenous infusion is a most common infusion time in Japan. Since the platinum agent is recognized as a linear drug in terms of pharmacokinetics, the infusion time does not affect the rate constants of the model in this study theoretically.

Pharmacological analysis of platinum

Sampling

For the pharmacological analysis, both serum and intraperitoneal fluid were obtained from all patients in both intravenous and intraperitoneal groups. For the patients in the intravenous group, 500 ml 5% dextrose was infused before intravenous carboplatin administration in order to obtain an intraperitoneal fluid collection. For both groups, intraperitoneal fluid and blood samples were obtained immediately and 1, 2, 4, 8, 12, and 24 h after

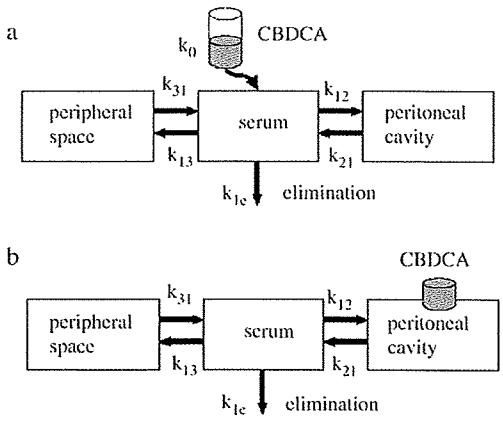

Fig. 1. The scheme of the three-compartment model of intravenous infusion (a, upper panel) or intraperitoneal administration (b, lower panel) of carboplatin (CBDCA).

carboplatin infusion. Intraperitoneal fluid and blood samples were centrifuged immediately at 1000 rpm for 10 min to remove cellular elements and then were centrifuged through Amicon Centrifo Cf-25 filter cones (25 kDa molecular cutoff, Amicon Corp., Lexington, MA) at 3000 rpm for 30 min to collect platinum in the filtrate. The samples were stored at −20°C until all the sample collections were completed. The platinum concentration was measured by flameless atomic absorption spectrometry according to the method of LeRoy et al. [11].

Mathematical model and analysis

The mathematical model of the pharmacokinetics of carboplatin was created by using differential equations. The theoretical three-compartment model is shown in Figs. 1a and b for intravenous and intraperitoneal carboplatin administration, respectively. The equations for these models are shown as follows.

The intravenous infusion model was as Eqs. (1)–(4)

$$\frac{dx_0}{dt} = -k_0, \tag{1}$$

$$\frac{dx_1}{dt} = k_0 - k_{12}x_1 - k_{13}x_1 - k_{1e}x_1 + k_{21}x_2 + k_{31}x_3, \tag{2}$$

$$\frac{dx_2}{dt} = k_{12}x_1 - k_{21}x_2, \tag{3}$$

$$\frac{dx_3}{dt} = k_{13}x_1 - k_{31}x_3. \tag{4}$$

The intraperitoneal infusion model was as Eqs. (5)–(7)

$$\frac{dx_1}{dt} = -k_{12}x_1 - k_{13}x_1 - k_{1e}x_1 + k_{21}x_2 + k_{31}x_3, \tag{5}$$

$$\frac{dx_2}{dt} = k_{12}x_1 - k_{21}x_2, \tag{6}$$

$$\frac{dx_3}{dt} = k_{13}x_1 - k_{31}x_3 \tag{7}$$

in which k_0 is the rate constant from the infusion bottle to the serum, k_{12} the rate constant from the serum to the intraperitoneal cavity, k_{13} the rate constant from the serum to the peripheral space, k_{1e} the elimination rate constant from the serum, k_{21} the rate constant from the intraperitoneal cavity to the serum, k_{31} the rate constant from the peripheral space to the serum, x_0 the amount of free platinum in the infusion bottle, x_1 the amount of free platinum in the serum, x_2 the amount of free platinum in the peritoneal cavity, x_3 the amount of free platinum in the peripheral space.

This model was solved by using the Runge–Kutta method with an original program using Mathematica software (Wolfram Research, Inc., Champaign, IL, USA) on a Macintosh computer. The rate constants were determined using the least square method to fit the sample data with the program.

Table 1
The measured area under the time concentration curve (AUC) of free platinum (Pt) for each patient

Case	Route	AUC (freePt in peritoneal cavity) (mg × min/ml)	AUC (freePt in serum) (mg × min/ml)
1	IP	113.00	2.79
2	IP	157.10	4.23
3	IP	21.60	3.87
4	IP	37.70	2.84
5	IP	61.86	2.51
6	IP	40.39	4.51
7	IP	25.24	2.44
8	IP	37.53	2.89
9	IP	43.22	2.27
10	IP	33.90	1.65
11	IP	14.90	1.50
	IP-mean	53.31	2.86
	IP-SD	43.38	0.98
12	IV	2.37	2.75
13	IV	3.57	2.48
14	IV	0.47	2.34
15	IV	0.67	1.91
16	IV	0.84	2.48
17	IV	4.66	2.76
18	IV	3.75	1.76
19	IV	5.64	3.56
20	IV	2.82	1.98
21	IV	4.58	2.86
22	IV	4.72	1.57
	IV-mean	3.10	2.40
	IV-SD	1.81	0.58

The value of the AUC in the serum is not statistically different between intraperitoneal administration (IP) and intravenous administration (IV). On the other hand, the value of the AUC in the peritoneal cavity is statistically higher by IP than by IV.

Results

Actual measurement of filtrated platinum AUC in the intraperitoneal and intravenous spaces after intraperitoneal or intravenous carboplatin administration

The actual filtrated platinum AUC of each patient in the intraperitoneal and intravenous spaces after intraperitoneal or intravenous carboplatin administration is summarized in Table 1. The mean intraperitoneal space AUC after intraperitoneal administration of carboplatin was approximately 17 times higher than that after intravenous administration (53.31 ± 43.38 mg × min/ml for intraperitoneal vs. 3.10 ± 1.81 mg × min/ml for intravenous, respectively). On the other hand, the filtrated platinum AUC in the intravenous space was not different after intraperitoneal administration or intravenous administration (2.86 ± 0.98 mg × min/ml and 2.40 ± 0.58 mg × min/ml, respectively). The reason of lower value of serum AUC of filtrated platinum even after intravenous administration of carboplatin at AUC of 6 appeared to be because of the lower molecular weight of filtrated platinum (195.09) that is approximately half of carboplatin (371.25). Therefore, measured mean value of filtrated platinum AUC of 3.10 mg × min/ml is reasonable after carboplatin was intravenously administered at the target AUC of 6 mg × ml/min.

Mathematical model analysis

The calculated rate constants (k_{21}, k_{12}, k_{13}, k_{31}, and k_{1e}) and AUC of filtrated platinum in the intraperitoneal and intravenous spaces for each patient after intraperitoneal or intravenous carboplatin administration are listed in Table 2. The means and standard deviations of rate constants and AUC are also shown. The mean calculated AUC of the filtrated platinum in the intraperitoneal space after intraperitoneal administration of carboplatin was 57.10 ± 17.45 mg × min/ml and 3.65 ± 2.95 mg × min/ml after intravenous administration. The mean calculated AUC of the filtrated platinum in the intravenous space after intraperitoneal or intravenous carboplatin administration was 2.92 ± 0.97 and 2.52 ± 0.80 mg × min/ml, respectively. These values were comparable with the measured values summarized in Table 1, and the calculated curves were fitted well with sampling

Table 2
The calculated rate constants and calculated area under the time concentration curve (AUC) in the peritoneal cavity and in the serum for each patient

Case	Route	Body weight (kg)	CBDCA (mg/body)	k_{21} (h^{-1})	k_{12} (h^{-1})	k_{13} (h^{-1})	k_{31} (h^{-1})	k_{1e} (h^{-1})	AUC (freePt in peritoneal cavity) (mg × min/ml)	AUC (freePt in serum) (mg × min/ml)
1	IP	42.0	563	0.85	0.55	16.5	1.3	3.4	48.51	2.76
2	IP	42.5	602	0.60	0.55	2.5	0.5	2.5	77.18	3.97
3	IP	58.5	763	1.35	0.55	2.5	0.5	2.2	44.54	4.15
4	IP	58.0	706	0.85	0.55	4.5	0.5	4.0	59.57	2.13
5	IP	51.5	779	0.60	0.05	2.5	0.3	4.3	82.82	2.46
6	IP	49.4	693	0.60	0.05	6.5	0.9	2.2	74.48	4.65
7	IP	49.0	671	1.10	0.55	0.5	0.1	3.4	44.64	2.80
8	IP	48.5	538	0.85	0.55	24.5	2.9	2.5	48.69	3.11
9	IP	52.0	878	2.10	7.55	8.5	0.3	4.6	68.67	2.52
10	IP	52.0	838	2.10	7.55	20.5	0.7	6.4	54.73	1.76
11	IP	41.1	510	3.35	7.55	12.5	0.5	4.9	24.28	1.76
	IP-mean	49.5	685.5	1.3	2.4	9.2	0.8	3.7	57.1	2.9
	IP-SD	5.9	122.6	0.9	3.3	8.2	0.8	1.3	17.5	1.0
12	IV	30.0	336	0.35	0.05	24.5	1.9	2.2	1.36	3.55
13	IV	54.0	754	0.10	0.05	24.5	1.1	4.6	4.84	2.12
14	IV	44.0	803	0.60	0.05	24.5	0.9	5.8	0.73	2.20
15	IV	62.0	699	0.60	0.05	24.5	1.1	4.9	0.75	1.61
16	IV	57.0	888	0.85	0.55	24.5	1.1	5.2	6.96	2.10
17	IV	49.0	940	0.35	0.05	24.5	1.9	3.7	2.29	3.63
18	IV	48.2	887	0.35	0.05	24.5	1.1	5.8	1.38	2.22
19	IV	68.0	865	0.10	0.05	16.5	0.7	2.5	9.36	3.42
20	IV	52.0	1001	0.35	0.05	24.5	1.3	5.8	1.55	2.32
21	IV	59.0	841	2.10	0.55	24.5	1.3	3.1	4.45	3.20
22	IV	59.0	784	0.60	0.55	24.5	0.9	7.0	6.46	1.33
	IV-mean	52.9	799.8	0.6	0.2	23.8	1.2	4.6	3.6	2.5
	IV-SD	10.2	175.8	0.6	0.2	2.4	0.4	1.5	3.0	0.8

These constants in the simultaneous different equations were solved by the Runge–Kutta method to fit to the sample data. The AUC was calculated using the mathematical model by integrating until the time of the final sampling of each patient. The calculated AUC are not statistically different from the measured AUC shown in Table 1. As the measured data shown in Table 1, the value of the AUC in the serum is not statistically different between intraperitoneal administration (IP) and intravenous administration (IV). The value of the AUC in the peritoneal cavity is statistically higher by IP than by IV. (k_{12}, rate constant from the serum to the intraperitoneal cavity; k_{13}, rate constant from the serum to the peripheral space; k_{1e}, elimination rate constant from the serum; k_{21}, rate constant from the intraperitoneal cavity to the serum; k_{31}, rate constant from the peripheral space to the serum.)

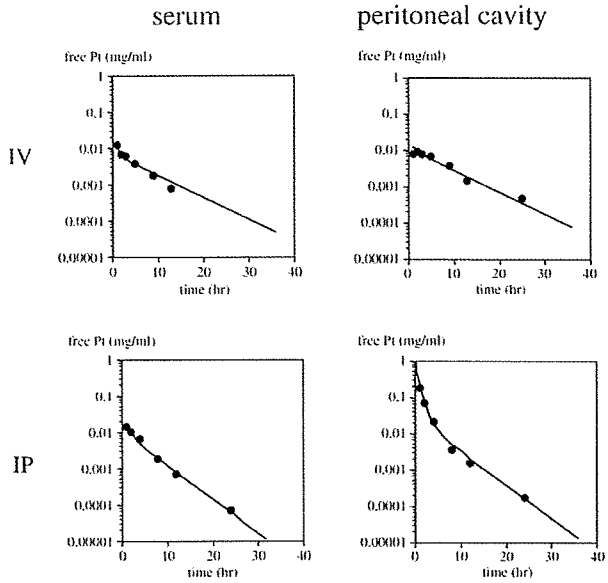

Fig. 2. Cases of intravenous administration (upper panel) and of intraperitoneal administration (lower panel) of carboplatin. The concentration of the filtrated platinum in the serum (left panel) and in the peritoneal cavity (right panel) is shown. The sampling data shown in closed circles are fit well by a combination of rate constants of the differential equations.

points of each patient as shown in Fig. 2. Therefore, it could be suggested that the mathematical model we proposed in this study can estimate the intraperitoneal AUC of the filtrated platinum after intraperitoneal or intravenous administration of carboplatin, when the patient's weight and total carboplatin dose were known.

Discussion

To the best of our knowledge, this is the first pharmacological study that compared the pharmacokinetic parameters of filtrated platinum and AUC in both intravenous and intraperitoneal spaces after intraperitoneal or intravenous administration of carboplatin. Several studies have suggested the advantage of intraperitoneal administration of carboplatin by measuring pharmacokinetics in peritoneal fluid and plasma only after intraperitoneal administration [12,13]. As shown in this study, the AUC of filtrated platinum in the intravenous space had the same value regardless of whether the intraperitoneal or intravenous administration routes of carboplatin were used. This result is an important message suggesting that intraperitoneal carboplatin therapy is not only suitable for the regional intraperitoneal therapy but also is one of the routes for systemic chemotherapy that can maintain the same AUC of filtrated platinum while providing a 17 times higher level of filtrated platinum AUC in the intraperitoneal cavity.

Usually, the advantage of the intraperitoneal chemotherapy has been described as an intraperitoneal regional therapy that could potentially reduce the systemic toxicities by maintaining extremely high intraperitoneal cavity/plasma ratio of the drug [7]. For example, the peak peritoneum/plasma concentration ratio of paclitaxel after intraperitoneal paclitaxel infusion is approximately 1000 [8], whereas the peritoneal/plasma ratio of AUC of carboplatin after intraperitoneal carboplatin infusion is approximately 30 [7]. Therefore, carboplatin is not an optimal drug for intraperitoneal chemotherapy if intraperitoneal chemotherapy is considered to be a regional therapy inside the intraperitoneal cavity. However, the present study suggests that intraperitoneal administration of carboplatin may be better than intravenous administration if the antitumor activity of carboplatin is based on its AUC, because intraperitoneal carboplatin administration provides a higher intraperitoneal platinum AUC while attaining the same intravenous platinum AUC as that obtained with intravenous carboplatin administration.

This pharmacological characteristic also suggests that intraperitoneal carboplatin administration may be as effective as or better than intravenous administration for patients with large volume residual disease, although intraperitoneal chemotherapy is usually indicated only for small size residual disease because the penetration of the agent is limited to a few millimeters. In fact, Fujiwara et al. reported a response rate of approximately 66% in their retrospective analysis of intraperitoneal carboplatin-based treatment, mostly combined with cyclophosphamide, in ovarian cancer [6]. This issue also must be confirmed in a prospective manner.

Another important issue to be considered in the future study is the status of intraperitoneal cavity. In this study, a wide variability was observed in the carboplatin pharmacokinetics of intraperitoneal space. This was probably because of the difference of intraperitoneal disease status such as degree of peritoneal carcinomatosis and/or volume of residual tumors. Information regarding status of intraperitoneal space should be included in the future clinical and pharmacological studies, idealistically by quantifying those parameters, so that identification of patient population that is truly benefited by the IP carboplatin treatment becomes possible.

In the present study, we created a mathematical model that enables us to describe the pharmacokinetics after administration of carboplatin intravenously or intraperitoneally. According to the computer simulation using this model, it was confirmed that platinum AUC in the serum after intraperitoneal carboplatin administration was the same as that after intravenous administration, when the same dose of carboplatin per kilogram was given.

The model can provide unique pharmacological information, such as the value of the AUC in the peripheral compartment or the platinum profile in each compartment as a function of time. Those calculated data can also be compared with clinical data of the patients, such as cytocidal effects and side effects. The analysis of the relationship

between the calculated data and the clinical data might bring us novel pharmacological information about chemotherapy. Thus, theoretically, the simulation using the model seems to allow the development of more adequate administration methods, which will be useful for patients and also for creating more reasonable chemotherapy regimens in clinical studies.

In conclusion, the present pharmacological analysis suggests that intraperitoneal infusion of carboplatin may be as effective as intravenous therapy for systemic disease, and also may be more effective for intraperitoneal disease such as ovarian, peritoneal, or fallopian tube cancer. This hypothesis must be confirmed by the future clinical randomized trial testing the efficacy of IP versus IV carboplatin administration. The mathematical model that we created may be useful to analyze the pharmacokinetic behavior of different types of anticancer agents that are administered intraperitoneally or intravenously.

Acknowledgments

Authors thank Ms. Hiroko Shirafuji for her excellent technical support. This study was presented at American Society of Clinical Oncology Meeting in 2004. This project was supported in part by a research grant provided by Bristol Japan.

References

[1] Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 1996;335:1950–5.

[2] Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:1001–7.

[3] Armstrong DK, Bundy BN, Baergen R, Lele SB, Walker J, Copeland LJ, et al. Randomized phase III study of intravenous (IV) paclitaxel and cisplatin versus IV paclitaxel, intraperitoneal (IP) cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group trial (GOG 172). Proc Am Soc Clin Oncol 2002 [Abstr # 803].

[4] du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003;95:1320–9.

[5] Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a gynecologic oncology group study. J Clin Oncol 2003;21:3194–200.

[6] Fujiwara K, Sakuragi N, Yoshida N, Suzuki S, Maehata K, Nishiya M, et al. First-line intraperitoneal carboplatin-based chemotherapy for 165 patients with epithelial ovarian carcinoma: results of long-term follow-up. Gynecol Oncol 2003;90:637–43.

[7] Markman M. Intraperitoneal chemotherapy. Semin Oncol 1991;18:248–54.

[8] Markman M, Francis P, Rowinsky E, Hakes T, Reichman B, Jones W, et al. Intraperitoneal taxol (paclitaxel) in the management of ovarian cancer. Ann Oncol 1994;5(Suppl 6):S55–8.

[9] Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989;7:1748–56.

[10] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.

[11] LeRoy AF, Wehling ML, Sponseller HL, Friauf WS, Solomon RE, Dedrick RL, et al. Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. Biochem Med 1977;18:184–91.

[12] DeGregorio MW, Lum BL, Holleran WM, Wilbur BJ, Sikic BI. Preliminary observations of intraperitoneal carboplatin pharmacokinetics during a phase I study of the Northern California Oncology Group. Cancer Chemother Pharmacol 1986;18:235–8.

[13] Elferink F, van der Vijgh WJ, Klein I, Bokkel Huinink WW, Dubbelman R, McVie JG. Pharmacokinetics of carboplatin after intraperitoneal administration. Cancer Chemother Pharmacol 1988;21:57–60.

ACADEMIC PRESS

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Gynecologic Oncology

Gynecologic Oncology 90 (2003) 637–643

www.elsevier.com/locate/ygyno

First-line intraperitoneal carboplatin-based chemotherapy for 165 patients with epithelial ovarian carcinoma: results of long-term follow-up

Keiichi Fujiwara,[a,*] Noriaki Sakuragi,[b] Sachiko Suzuki,[a] Nobutaka Yoshida,[c] Kenichiro Maehata,[a] Masashi Nishiya,[b] Takayuki Koshida,[b] Hideaki Sawai,[c] Eriko Aotani,[d] and Ichiro Kohno[a]

[a] *Department of Obstetrics and Gynecology, Kawasaki Medical School, Kurashiki-City 701-0192, Japan*
[b] *Department of Obstetrics and Gynecology, Hokkaido University, Sapporo, Japan*
[c] *Department of Obstetrics and Gynecology, Hiroshima City Hospital, Hiroshima, Japan*
[d] *Department of Nursing, Kawasaki University of Medical Welfare, Kurashiki, Japan*

Received 29 January 2003

Abstract

Objective. Currently, no long-term follow-up data are available on intraperitoneal (IP) carboplatin-based chemotherapy for ovarian carcinoma. In this study we evaluated retrospectively the survival and recurrence of a retrospective cohort of patients with epithelial ovarian cancer treated with first-line IP carboplatin-based therapy.

Methods. Records were reviewed of 174 patients with epithelial ovarian cancer who received IP carboplatin-based therapy between 1990 and 2000. All patients underwent surgical staging, and implantable port systems were placed regardless of residual tumor size. The pathological slides were submitted and reviewed, and then nine patients were excluded because of borderline malignancies ($n = 8$), and wrong histology ($n = 1$). Therefore, the records of 165 patients were analyzed for survival. Tumor grade was determined by the Universal grading system. Statistical analysis included tests for association between potential prognostic factors, and between prognostic factors and survival. Survival probabilities were estimated by Kaplan-Meier methods, and prognostic factors for survival were evaluated by a Cox regression model.

Results. The mean age of the patients was 53.7 years (range 21–83). The median follow-up was 41 months. The distribution by stage and histology was as follows: high risk (grade 2/3, clear cell, capsule rupture) stage I, 54; II, 21; III, 72; IV, 18; and serous, 75; clear cell, 30; mucinous, 27; endometrioid, 20; others, 13. The chemotherapy regimen was either carboplatin alone ($n = 22$) or in combination with cyclophosphamide ($n = 116$) or paclitaxel ($n = 27$). Catheter-related complications occurred in 16 (9.7%) cases. The chemotherapeutic response in 54 patients with measurable disease was 66.4%. The 5-year survival was 94.4% for stage I, and 87.9% for stage II. The median survival for optimal and suboptimal stage III/IV patients was 51 months and 34 months, respectively. The median survival of patients with stage III/IV disease was 51 months with carboplatin doses of 400 mg/m^2 or more, but it was only 25 months with carboplatin doses smaller than 400 mg/m^2. Poor prognostic factors, determined by Cox regression multivariate analysis, were clear cell histology ($P < 0.001$) and a carboplatin dose smaller than 400 mg/m^2 ($P = 0.002$).

Conclusions. Survival of patients who underwent carboplatin-based IP chemotherapy was excellent when the dose of carboplatin was higher than 400 mg/m^2. A prospective evaluation of IP carboplatin therapy with modern combination is warranted.

Keywords: Intraperitoneal chemotherapy; Ovarian cancer; Carboplatin; Cyclophosphamide; Paclitaxel

Introduction

The most characteristic feature of ovarian cancer is the intraperitoneal (IP) spread of disease at its early stages. Therefore, theoretically, IP chemotherapy is a reasonable approach in the treatment of ovarian cancer. In fact, there have been three large randomized phase III studies comparing IP to intravenous (IV) cisplatin-based chemotherapy in the United States. The first trial was published in 1996, demonstrating that IP cisplatin-based therapy was superior to IV therapy in terms of survival and toxicity in optimally debulked stage III ovarian cancer patients [1]. The second

* Corresponding author. Department of Obstetrics and Gynecology, Kawasaki Medical School, 577 Matsushima, Kurashiki-City 701-0192, Japan. Fax: +81-86-462-1199.
E-mail address: fujiwara@med.kawasaki-m.ac.jp (K. Fujiwara).

0090-8258/03/$ – see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/S0090-8258(03)00377-9

and third trials conducted by the Gynecologic Oncology Group also showed the survival advantage of the IP cisplatin-based regimen [2,3]. In spite of these favorable survival results for IP arms, the IP cisplatin-based chemotherapy has not been accepted as a standard treatment for ovarian cancer. Although the first trial demonstrated an improvement of both survival and toxicity in the IP arm, toxicities of IP arms in the second and third trials were significantly worse than for the IV arm. Additionally it appears that the complexity of the trial design of these two studies made it difficult to make a simple comparison of IP vs IV administration of cisplatin.

Therefore, it is necessary to create a simple and less toxic trial design to test the role of IP platinum agents. The platinum agent that is most likely to reduce the toxicity is carboplatin. However, despite the fact that many studies have shown that IV administration of carboplatin was as efficacious as cisplatin but less toxic [4–7], it has not become a standard agent for IP treatment. The reason for this is based on two studies. One of them was an animal experiment showing that approximately 10 times more carboplatin than cisplatin was required to obtain equivalent tissue platinum concentrations [8]. Based on this result, Markman et al. retrospectively analyzed their clinical data and showed that the response rate was better in cisplatin-based regimens [9]. Although they implied the necessity of performing a prospective randomized trial, to our knowledge it has never been tried. We felt that it was not reasonable to conclude that carboplatin is less effective than cisplatin based on the Markman study because: (1) this study was small and retrospective, and (2) the dose of carboplatin was too low (200–300 mg/m^2) compared to a large dose of cisplatin (100 mg/m^2). As our pharmacological data suggested that more than 2/3 of free platinum entered into the systemic circulation [10], we believed that IP carboplatin should produce reasonable responses if an appropriate dose was administered. In addition, it was theoretically justified that IP carboplatin therapy could be used as a route of systemic chemotherapy in patients with large residual tumors while exposing the tumor surface with extremely high concentration of carboplatin. Therefore, based on these theoretical considerations, routine administration of IP carboplatin has been our choice of therapy since 1990 for epithelial ovarian cancer patients regardless of residual tumor size.

This study aimed to evaluate retrospectively the survival and recurrence of a cohort of patients with epithelial ovarian cancer treated with first-line IP carboplatin-based therapy.

Patients and methods

Patients

In the three institutions, Kawasaki Medical School, Hokkaido University, and Hiroshima City Hospital, records were reviewed for those patients with epithelial ovarian cancer who had undergone primary surgery followed by placement of intraperitoneal port systems (IPS) and IP carboplatin-based chemotherapy. In these institutions, the physicians explained the potential benefit of IP carboplatin administration and the written consents have been obtained prior to the surgery. We identified 174 patients who were eligible for this study. Pathological slides of these patients were reviewed again, and nine of them were excluded: eight of them were borderline malignancies, and one had wrong histology (immature teratoma). Therefore, 165 cases (43, 48, and 74 cases in the three institutions, respectively) were eligible to be analyzed.

Statistical analysis

Statistical analysis included tests for associations between potential prognostic factors and between prognostic factors and overall survival or progression-free survival. The time to treatment failure after IP therapy was calculated from the time of initiation of primary surgery to radiographic or clinical evidence of recurrence. Survival probabilities were estimated by Kaplan-Meier methods [11]. For the factor analysis, univariate analyses were performed using the log-rank test [12], and multivariate analyses were performed using the Cox regression model [13].

Results

Patient characteristics

Patient characteristics, such as clinical stage, histology, tumor grade, the percentages of patients who had residual disease smaller or larger than 2 cm, respectively in stage III/IV patients, and chemotherapeutic regimen and course number, are summarized in Table 1. The mean age of patients was 54 years (range 21–83). More than half of the patients were FIGO stage III or IV and 32.7% of patients had high-risk (capsule rupture, grade 2/3, and/or clear cell histology) stage I disease. Serous histology was the most predominant (45.5%), and clear cell carcinomas comprised 18.2% of the cases. Most cases (74%) had moderately or poorly differentiated disease. In the 90 stage III or IV cases, 58.9% of them had residual disease $\geq$2 cm.

The median number of chemotherapy cycles was six and the median number of IP cycles was five, suggesting that IP therapy was well tolerated. Most patients underwent combination therapy with cyclophosphamide because paclitaxel was not commercially available in Japan until 1998. The choice between using carboplatin alone or combination therapy was made by the physician, mainly based on the stage and/or status of residual disease.

Table 1
Patient characteristics

Age	Mean 53.7	Range 21–83
Performance status	Number	Percentage
0	80	48.5%
1	72	43.6%
2	13	7.9%
Stage	Number	Percentage
I	54	32.7%
II	21	12.7%
III	72	43.6%
IV	18	11.0%
Histology	Number	Percentage
Serous	75	45.5%
Mucinous	27	16.4%
Endometrioid	20	12.1%
Clear cell	30	18.2%
Adenocarcinoma	5	3.0%
Undifferentiated	7	4.2%
Mixed	1	0.6%
Tumor grade		
1	43	26%
2	59	36%
3	63	38%
Stage III/IV		
Residual disease (n = 90)		
<2cm	37	41.1%
≥2cm	53	58.9%
Chemotherapy course	Median	Range
Total	6	1–35
IP chemotherapy	5	1–18
Chemotherapy regimen		
IP carboplatin alone	22	13.3%
With cyclophosphamide	116	70.3%
With paclitaxel	27	16.4%

Drug administrations

IP carboplatin was administered either as a drip infusion or bolus infusion depending on the institution. When given as a drip infusion, carboplatin was diluted in 500 – 1000 ml 5% glucose or saline solution and administered as 2–3 h infusion. When given as a bolus infusion, 500 – 1000 ml glucose or saline solution was administered before bolus carboplatin was given. Dose of carboplatin was determined by the institutions' policy, either calculated based on body surface area, or Calvert formula, or simply using a fixed dose for every patient in the institution.

When cyclophosphamide was combined it was administered as a 1–2 h intravenous drip infusion after IP carboplatin administration. When paclitaxel was combined, it was administered as a 3 h intravenous drip infusion before IP carboplatin was administered. The median dose of cyclophosphamide in this study was 500 mg/m^2 and median dose of paclitaxel was 175 mg/m^2.

All treatments were repeated with 3–4 weeks interval when adverse events were acceptable.

Adverse events

Adverse events are summarized in Table 2. Overall bone marrow toxicities were acceptable. Incident of grade 3/4 neutropenia was not different between carboplatin dose <400 mg/m^2 and ≥400 mg/m^2. However, platelet toxicity was significantly related to the dose of carboplatin.

IP chemotherapy was terminated in 24 out of 165 patients (14.5%), but IP catheter-related cessation was less than 10%. At the time cathter-related complication occurred, IP cathter was removed and IP therapy was terminated and converted to intravenous therapy.

Second look surgery

There were 18 patients who underwent second look surgery. The purpose of second look surgery in this study was to confirm chemotherapeutic response either because there were no measurable disease at the conclusion of initial surgeries (n = 11) or because the tumor ≥2 cm at the conclusion of initial surgery became too small to measure after chemotherapy (n = 7). The residual disease status at the conclusion of initial surgery was microscopic in eight of the former 11 patients and three patients had macroscopic residual disease measuring <2 cm. In the eight patients with microscopic residual disease, six patients became negative for second look. Two of three patients with residual disease <2 cm became negative for second look findings. In the latter seven patients with residual tumors >2 cm at the conclusion of initial surgery, four patients became negative for second look, two had microscopic disease, and one patient had tumors measuring 1.5 cm.

Survival

Table 3 summarizes the comparison of median progression-free survival (PFS) and median overall survival (OS) by various factors. The clinical stage was a significant prognostic factor on PFS and OS, as shown in Fig. 1 (P < 0.0001). Because the number of events in stage I/II patients was limited, we did not perform the factorial comparison in this population except for histological differences.

In this series, neither PFS nor OS showed statistically significant differences in relation to the size of residual disease in stage III/IV patients, although PFS and OS were worse in patients with larger residual disease.

A comparison of the survival in relation to the administered dose of carboplatin showed that there was no difference in stages I or II patients between those who received carboplatin <400 mg/m^2 or ≥400 mg/m^2 (P = 0.2485). However, in stages III/IV, cases, survival was significantly better in patients who received carboplatin ≥400 mg/m^2 (median survival = 51 months) than in those receiving <