# Impact of maintenance chemotherapy on disease-free survival in patients with stage Ic and II epithelial ovarian cancer

**N. Tanaka[1], H. Matsui[1], Y. Nagai[2], K. Suzuka[3], K. Seki[1], S. Sekiya[1,3]**

*[1]Department of Reproductive Medicine; [2]Department of Molecular Pathology, Chiba University Graduate School of Medicine, Chiba; and [3]Department of Obstetrics and Gynecology, Chiba University Hospital, Chiba (Japan)*

## Summary

*Purpose of investigation:* To evaluate the impact on disease free survival (DFS) with maintenance chemotherapy following complete surgery and adjuvant chemotherapy in patients with stage Ic and II epithelial ovarian cancer by a retrospective study.

*Methods:* One hundred and forty patients with stage Ic and stage II epithelial ovarian cancer were classified into three groups according to the modality of maintenance chemotherapy (no therapy, oral or intravenous administration of anti-cancer drugs). DFS was compared among the three groups, and independent predictive factors for relapse were analyzed.

*Results:* There were no statistically significant differences in DFS among the three groups for either stage Ic or II cancers, stage Ic and stage II. Multivariate analysis revealed that independent predictive factors for relapse were stage II ($p = 0.004$) in all patients and less than three cycles of adjuvant chemotherapy in stage II patients ($p = 0.015$).

*Conclusion:* Maintenance chemotherapy had no impact on DFS in patients with stage Ic or II epithelial ovarian cancer.

*Key words:* Epithelial ovarian cancer; Maintenance chemotherapy; Disease-free survival.

## Introduction

The 5-year survival rate of women with early stage ovarian cancer is much greater than that of women with advanced disease when accurate and comprehensive surgical staging is done. In particular, several large studies [1-3] indicate that stage Ia and Ib patients with well or moderately differentiated histology have good prognoses and require no adjuvant chemotherapy. On the other hand, these studies show that stage Ic and II patients and stage Ia and Ib patients with poorly differentiated histology or clear cell histology have a 30% to 40% risk of relapse and a 25% to 30% chance of dying within the first five years after initial surgery. These ovarian cancer patients at high risk for relapse are candidates for clinical trials evaluating adjuvant therapies. Results from a Gynecologic Oncology Group (GOG) trial (GOG 95) and several international trials [2, 3] indicate that platinum-based adjuvant chemotherapy reduces the risk of relapse for high-risk, early ovarian cancer patients, although the overall long-term survival benefits of adjuvant chemotherapy remain questionable.

In recent years, several reports [4, 5] show that intermittent chemotherapy prolongs remission and improves overall survival for advanced ovarian cancer patients. However, to the best of our knowledge, no reports have addressed whether or not intermittent chemotherapy prevents relapse or improves overall survival for high-risk, early stage ovarian cancer patients. Thus, we conducted a retrospective study to evaluate the effectiveness of intermittent chemotherapy following the completion of surgery and adjuvant chemotherapy for stage Ic and II epithelial ovarian cancer patients.

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## Materials and Methods

From 1985 through 1998, 140 patients with stage Ic or II epithelial ovarian cancer who had undergone initial surgery followed by adjuvant chemotherapy at Chiba University Hospital and six community hospitals were evaluated in this retrospective study. All patients met the following eligibility criteria: 1) no residual tumors at initial surgery; 2) adjuvant chemotherapy with more than two consecutive courses of platinum-containing therapeutics; 3) no relapse within three months after the completion of adjuvant chemotherapy. Patients were classified into three groups as follows: NO-group, patients who received no maintenance chemotherapy; PO-group, patients who were orally administered carboquone [6] or UFT (a 1:4 mixture of tegafur and uracil) (Taiho Pharmaceutical Co., Tokyo) [7] for more than three months (within the previous 2 years) as maintenance chemotherapy; IV-group, patients who received repeated chemotherapy identical to the previous adjuvant chemotherapy at 3-month intervals within two years following the initial adjuvant chemotherapy.

All initial operations were cytoreductive with no macroscopical residuum, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, appendectomy, or pelvic or paraaortic lymphnode sampling. Second-look surgery was not routinely performed, and 19 out of 140 patients received second-look operations after adjuvant chemotherapy, and no recurrence was confirmed in the abdominal and pelvic cavities. Adjuvant chemotherapy regimens included either cisplatin or carboplatin, as detailed in Table 1. Patient characteristics and all follow-up data were verified by hospital medical records.

Clinical staging of ovarian cancer was determined according to the International Federation of Gynecologists and Obstetricians (FIGO) staging system. All pathological materials for this study were reviewed by at least three pathologists at Chiba University School of Medicine. Histologic subtyping for individuals was performed according to the classification of the World Health Organization [8], and the histopathologic grading was determined by the GOG grading system [9]. When histolo-

Table 1. — *Patient characteristics.*

| | Total (n = 140) | NO-group (n = 94) | PO-group (n = 25) | IV-group (n = 21) | [h]p value |
|---|---|---|---|---|---|
| Age (yr): median (range) | 50(16-75) | 50(26-75) | 49(16-69) | 55(24-67) | 0.49 |
| FIGO stage | | | | | 0.18 |
| Ic | 91 | 63 | 17 | 11 | |
| IIa | 5 | 5 | 0 | 0 | |
| IIb | 6 | 4 | 2 | 0 | |
| IIc | 38 | 22 | 6 | 10 | |
| Histologic subtype | | | | | 0.30 |
| Serous | 44 | 33 | 7 | 4 | |
| Macinous | 32 | 22 | 7 | 3 | |
| Endometrioid | 36 | 21 | 5 | 10 | |
| Clear cell | 28 | 18 | 6 | 4 | |
| Histologic grade | | | | | 0.66 |
| 1 | 58 | 41 | 9 | 8 | |
| 2 | 19 | 11 | 3 | 5 | |
| 3 | 4 | 3 | 0 | 1 | |
| [a]ND | 59 | 39 | 13 | 7 | |
| Adjuvant chemotherapy | | | | | 0.06 |
| [b]CAP (CP) | 77 | 54 | 11 | 12 | |
| [c]IAJ (IJ) | 41 | 19 | 13 | 9 | |
| [d]CVpP/VpP | 8 | 7 | 1 | 0 | |
| [e]J/Paclitaxel | 7 | 7 | 0 | 0 | |
| [f]P/Camptothecin | 3 | 3 | 0 | 0 | |
| [g]p | 4 | 4 | 0 | 0 | |
| Adjuvant chemotherapy cycles received: median (range) | 3(2-9) | 4(2-9) | 3(3-5) | 3(3-6) | 0.13 |

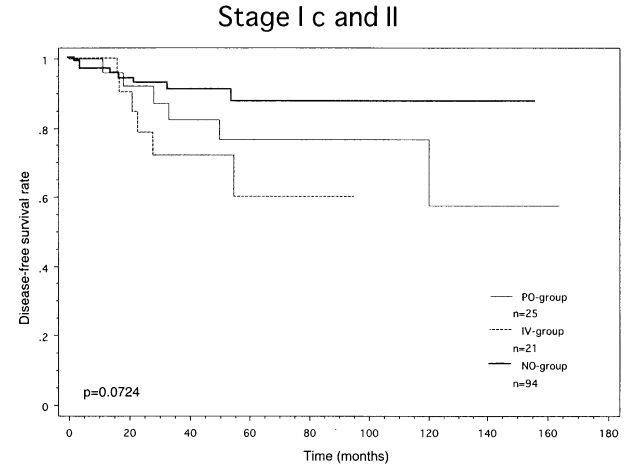
[a]ND: Not determined; [b]CAP (CP): Cyclophosphamide/Anthracyclin/cisplatin (Cyclophosphamide/cisplatin); [c]IAJ (IJ): Ifosfamide/Anthracyclin/carboplatin (Ifosfamide/carboplatin); [d]CVpP (VpP): Cyclophosphamide/VP-16/cisplatin (VP-16/cisplatin); [e]J/Paclitaxel: carboplatin/Paclitaxel; [f]P/Topotecan: cisplatin/camptothecin; [g]P: cisplatin only; [h]p-value: Monte Carlo method, except Scheffe's method for age distribution.

gic grading of a case was inconsistent among pathologists or the histologic subtype was clear cell adenocarcinoma , cases were placed in the 'ND (not determined)' category.

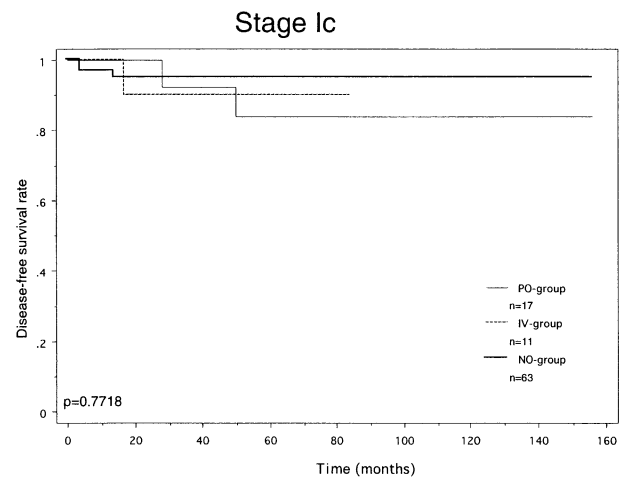
Homogeneity of distribution of FIGO stages, histologic subtypes and grades, and regimens of adjuvant chemotherapy among the three groups were compared using the Monte Carlo method [10]. Age distribution among individual groups was compared using Scheffe's method [11]. Disease-free survival (DFS) was calculated as the time from initial surgery to the day when recurrent focus was clinically detected, and DFS was selected as the endpoint in this study.

Survival curves were constructed using the Kaplan-Meier method [12], and differences between curves were tested using the Log-rank test. The Cox proportional hazard model [13] was used in both univariate and multivariate analyses.

All p values less than 0.05 were considered statistically significant. Confidence intervals (CI) were calculated with 95% limits. Statistical analyses were performed using the statistical software package, SPSS 10.0J (SPSS Inc., Chicago, IL).




1A

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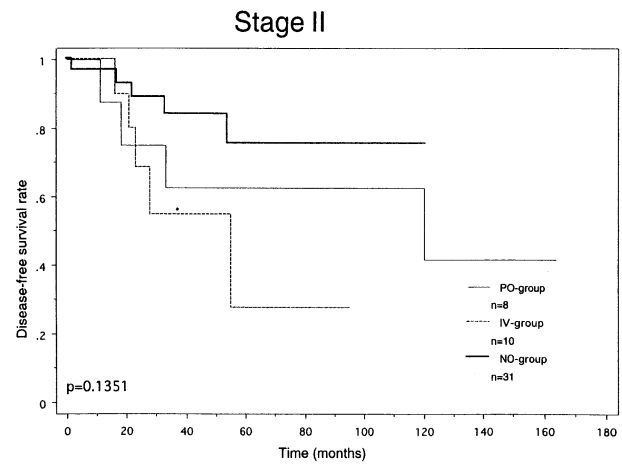


1C

Figure 1A, B, C. — Disease-free survival of stage Ic and II (A), stage Ic (B) and stage II (C) ovarian cancer patients subdivided by treatment group.
NO-group, no maintenance chemotherapy. PO-group, oral administration of anti-cancer drugs for maintenance chemotherapy. IV-group, intravenous administration of anti-cancer drugs for maintenance chemotherapy. Each p-value was calculated by the Log-rank test.

## Results

Characteristics of the 140 patients are shown in Table 1. There were no significant differences in the FIGO stages, histologic subtypes, grades, cycle number or regimens of adjuvant chemotherapy among the three groups. Figures 1 a, b, and c show disease-free survival curves for the three groups (NO-, PO- and IV-groups) in stage Ic and II, and stage Ic and stage II patients, respectively. In stage Ic and II patients, the mean DFS (equal to the area under the DFS curve for relapse cases) and 95% confidence interval (CI) of NO-, PO- and IV-groups were 140 months (CI:129-151), 124 (98-151) and 70 (53-86), respectively. As for stage Ic patients, the mean DFS and CI for NO-, PO- and IV-groups were 148 (140-157), 137 (11-161) and 77 (65-90), respectively, and in stage II patients, those of NO-, PO- and IV-groups were 99 (82-116), 101 (55-147) and 51 (28-75), respectively. There were no statistically significant differences for DFS among the three groups for stage Ic and II (log rank, p = 0.072), or stage Ic (p = 0.772) and stage II (p = 0.135).

Furthermore, the Cox proportional hazard model was applied to univariate and multivariate analyses in order to determine prognostic factors associated with DFS in this study group. As shown in Table 2A, stage (stage II vs stage Ic, Hazard Ratio (HR): 4.2 (95% CI: 1.611-10.946), p = 0.003) and histologic grade (grade III vs grade I, HR: 12.979 (2.514-67.008), p = 0.015) were significant prognostic factors for DFS in stage Ic and II patients by univariate analysis, and the only significant prognostic factors for DFS by multivariate analysis was stage (stage II vs stage Ic, HR: 4.127 (1.555-10.949), p = 0.004). In stage Ic patients, no significant prognostic factors for DFS were determined by univariate or multivariate analysis (Table 2b). Histologic grade might predict prognostic factors for DFS, but was not statistically significant by either univariate (p = 0.063) and multivariate (p = 0.065) analysis. In stage II patients, adjuvant chemotherapy cycles were significant prognostic factors for DFS by both univariate ( less than 3 cycles vs more than 4 cycles, HR: 3.929 (1.222-12.628), p = 0.022) and multivariate analysis (less than 3 cycles vs more than 4 cycles, HR: 4.280 (1.332-13.759), p = 0.015) (Table 2c).

Concerning maintenance chemotherapy, univariate analysis confirmed that PO- and IV- groups were not statistically significant prognostic factors for DFS (PO- vs NO-group, HR: 1.962 (0.672-5.726); IV- vs NO-group, HR: 3.217 (1.111-9.312), p = 0.091 in stage Ic and stage II) / PO- vs NO-group, HR 1.863 (0.307-11.303); IV- vs NO-group, HR: 1.616 (0.168-15.591), p = 0.778 in stage I / PO- vs NO-group, HR: 2.048 (0.516-8.134); IV- vs NO-group, HR: 3.327 (0.955-11.589), p = 0.164 in stage II) (Tables 2a, 2b and 2c).

## Discussion

The goal of maintenance chemotherapy for ovarian cancer patients is to prolong remission status after adjuvant chemotherapy and to prevent local and systemic relapse. Recently, several authors have demonstrated the effectiveness of maintenance chemotherapy for advanced [4, 5] and recurrent [14] ovarian cancer patients, although all of these studies were retrospective and were construc-

Table 2a. — *Univariate and multivariate analyses of prognostic factors on disease-free survival in stage Ic and II ovarian cancer patients.*

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | p-value | Hazard ratio | Confidence interval | p-value | Hazard ratio | Confidence interval |
| Age | 0.352 | 1.021 | 0.977-1.067 | | | |
| Stage | 0.003 | | | 0.004 | | |
| I | | 1.000 | Ref[a] | | 1.000 | Ref |
| II | | 4.200 | 1.611-10.946 | | 4.127 | 1.555-10.949 |
| Histologic subtype | 0.686 | | | | | |
| Serous | | 1.000 | Ref | | | |
| Mucinous | | 0.566 | 0.149-2.149 | | | |
| Endometrioid | | 0.645 | 0.193-2.148 | | | |
| Clear cell | | 1.162 | 0.374-3.610 | | | |
| Histologic grade | 0.015 | | | 0.089 | | |
| 1 | | 1.000 | Ref | | 1.000 | Ref |
| 2 | | 1.008 | 0.253-4.015 | | 0.876 | 0.217-3.530 |
| 3 | | 12.979 | 2.514-67.008 | | 7.727 | 1.489-40.097 |
| ND | | 1.049 | 0.380-2.896 | | 1.196 | 0.432-3.323 |
| Chemotherapy cycles | 0.471 | | | | | |
| 3 ≥ | | 1.404 | 0.558-3.534 | | | |
| 4 ≤ | | 1.000 | Ref | | | |
| Maintencance chemotherapy | 0.091 | | | | | |
| No-group | | 1.000 | Ref | | | |
| PO-group | | 1.962 | 0.672-5.726 | | | |
| IV-group | | 3.217 | 1.111-9.312 | | | |

Ref[a]: reference

Table 2b. — *Univariate and multivariate analyses of prognostic factors on disease-free survival in stage Ic ovarian cancer patients.*

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | p-value | Hazard ratio | Confidence interval | p-value | Hazard ratio | Confidence interval |
| Age | 0.302 | 0.962 | 0.893-1.036 | | | |
| Histologic subtype | 0.700 | | | | | |
| Serous | | 1.000 | Ref[a] | | | |
| Mucinous | | 2.069 | 0.187-22.941 | | | |
| Endometrioid | | 1.001 | 0.062-16.049 | | | |
| Clear cell | | 3.269 | 0.295-36.250 | | | |
| Histologic grade | 0.063 | | | 0.065 | | |
| 1 | | 1.000 | Ref | | 1.000 | Ref |
| 2 | | 1.591 | 0.144-17.578 | | 1.549 | 0.140-17-114 |
| 3 | | 46.540 | 2.394-904.692 | | 45.313 | 2.331-880.822 |
| ND | | 0.947 | 0.133-6.725 | | 0.922 | 0.130-6.547 |
| Chemotherapy cycles | 0.455 | | | | | |
| 3 ≥ | | 0.541 | 0.108-2.716 | | | |
| 4 ≤ | | 1.000 | Ref | | | |
| Maintencance chemotherapy | 0.778 | | | | | |
| No-group | | 1.000 | Ref | | | |
| PO-group | | 1.863 | 0.307-11.303 | | | |
| IV-group | | 1.616 | 0.168-15.591 | | | |

Ref[a]: reference

Table 2c. — *Univariate and multivariate analyses of prognostic factors on disease-free survival in stage II ovarian cancer patients.*

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | p-value | Hazard ratio | Confidence interval | p-value | Hazard ratio | Confidence interval |
| Age | 0.620 | 1.016 | 0.954-1.083 | | | |
| Histologic subtype | 0.806 | | | | | |
| Serous | | 1.000 | Ref[a] | | | |
| Mucinous | | 0.347 | 0.043-2.834 | | | |
| Endometrioid | | 0.897 | 0.225-3.574 | | | |
| Clear cell | | 0.905 | 0.227-3.604 | | | |
| Histologic grade | 0.579 | | | | | |
| 1 | | 1.000 | Ref | | | |
| 2 | | 0.739 | 0.138-3.967 | | | |
| 3 | | 4.166 | 0.459-37.775 | | | |
| ND | | 1.089 | 0.330-3.588 | | | |
| Chemotherapy cycles | 0.022 | | | 0.015 | | |
| 3 ≥ | | 3.929 | 1.222-12.628 | | 4.280 | 1.332-13.759 |
| 4 ≤ | | 1.000 | Ref | | 1.000 | Ref |
| Maintencance chemotherapy | 0.164 | | | | | |
| No-group | | 1.000 | Ref | | | |
| PO-group | | 2.048 | 0.516-8.134 | | | |
| IV-group | | 3.327 | 0.955-11.589 | | | |

Ref[a]: reference

ted with small numbers of patients. Inoue *et al.* [4] reported that cyclic PAC chemotherapy, in which the PAC regimen consisting of cisplatin, doxorubicin and cyclophosphamide was administrated periodically for 15 months after cytoreductive surgery, improved the overall suvival rates for stage Ic-IV ovarian cancer patients, compared with the control group with no therapy after adjuvant chemotherapy. Umesaki *et al.* [5] showed that intermittent cisplatin administration as consolidation therapy increased the 5-year survival rate for stage III ovarian cancer patients, compared with the control group. Eltabbakh *et al.* [14] reported that prolonged salvage and maintenance chemotherapy extended the disease-free interval among patients with platinum-sensitive recurrent epithelial ovarian cancer who were responsive to salvage chemotherapy.

On the other hand, there are only a few reports [6, 7, 15] showing the efficacy of orally administered anti-

cancer drugs for early and advanced cases of ovarian cancer patients in the maintenance of chemotherapy. There are no reports, however, concerning intermittent intravenous chemotherapy and the oral administration of anti-cancer drugs in maintenance chemotherapy to prevent relapse and improve the overall survival for high risk cases of early ovarian cancer patients. Thus, we conducted this retrospective study to evaluate the effectiveness of maintenance chemotherapy following surgery and adjuvant chemotherapy for stage Ic and II epithelial ovarian cancer patients.

Our results show no statistically significant differences for DFS among the three groups in both stage Ic and II, and stage Ic and stage II. Patients in the NO-group appeared to have the longest disease-free survival time among the three groups, especially among stage II cases, although the differences were not statistically significant. According to our multivariate analysis, less than three cycles of adjuvant chemotherapy was a significanct factor which has shortened DFS time in stage II cases, compared with more than four cycles of adjuvant chemotherapy. This result suggests that more than four cycles of adjuvant chemotherapy are effective in preventing relapse of stage II ovarian cancer. Gershenson *et al.* [16] indicated that optimally debulked, stage III or IV ovarian cancer patients with a planned treatment course of 12 cycles of chemotherapy had a significantly longer progression-free survival time than those with a planned course of six cycles. However, it remains to be determined how many cycles of adjuvant chemotherapy are optional for high risk, early ovarian cancer patients, although this question may soon be answered by the ongoing GOG 157 trial, which is a randomized phase III trial comparing the adjuvant administration of paclitaxel/carboplatin for three cycles versus six cycles in patients with high-risk, early stage ovarian cancer [17].

As for histologic subtype, especially clear cell histology, it is controversial whether or not clear cell subtype has prognostic significance [18]. Our results indicate that the clear cell subtype was not an independent factor predicting relapse in either stage Ic or II. In stage Ic cases, our multivariate analysis showed that histologic grade III tumors might be an independent prognostic factor predicting relapse, compared with grade I tumors, although the results were not statistically significant. A number of studies [18-21] have shown that tumor grade is an important independent prognostic factor in stage I ovarian cancer, as grade I tumors are associated with a 90% relapse-free survival rate in contrast to a 30% relapse-free survival rate for grade III tumors.

Paclitaxel is among the most efficacious of agents available for ovarian cancer and this drug in combination with a platinum agent is currently considered to be one of the more promising adjuvant chemotherapy regimens [17]. Only seven cases in this study received adjuvant and maintenance chemotherapy including paclitaxel, thus we were unable to evaluate the effectiveness of paclitaxel-based adjuvant and maitenance chemotherapy for high-risk, early-stage ovarian cancer patients. Randomized prospective trials including ongoing GOG 157 studies will better help identify more suitable adjuvant and maintenance chemotherapies towards preventing relapse and improving overall survival rates.

## Conclusion

Maintenance chemotherapy had no impact on DFS in patients with stage Ic or II epithelial ovarian cancer, though these results warrant confirmation by prospective randomized studies.

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Address reprint requests to:
N. TANAKA, M.D., PH.D.,
Department of Reproductive Medicine,
Chiba University Graduate School of Medicine,
1-8-1 Inohana, Chuo-ku, Chiba City,
Chiba 260-8670 (Japan)

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