Relationship between usefulness of irinotecan and pegylated liposomal doxorubicin therapy and the UGT1A1 genotype in patients with recurrent ovarian cancer (TGCU 104 study)

T. Shoji¹, E. Takatori¹, M. Kagabu¹, M. Futagami², Y. Yokoyama², H. Tokunaga³, N. Yaegashi³, T. Ohta⁴, T. Watanabe⁵, T Sugiyama⁶

¹Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka 020-8505
²Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, Hirosaki
³Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai
⁴Department of Obstetrics and Gynecology, Yamagata University Faculty of Medicine, Yamagata
⁵Department of Obstetrics and Gynecology, Fukushima Medical University School of Medicine, Fukushima
⁶Department of Obstetrics and Gynecology, Takagi Hospital, Okawa (Japan)

Summary

Objective: The authors investigated the relationship between the usefulness of CPT-11 + PLD combination therapy and the UGT1A1 genotype. Materials and Methods: Forty-one patients who provided informed consent were divided into the following two groups according to UGT1A1 genotypes: wild type and non-wild type. Adverse events, antitumor effect, and outcomes were compared between these two groups. Results: Twenty-three patients were wild type and 18 were non-wild type for UGT1A1. A total of 94 and 73 treatment cycles were prescribed to the wild-type and non-wild-type groups, respectively. No significant differences in the incidence of any grade 3 or higher adverse events were observed between the two groups. However, the next treatment cycle was postponed in 9.6% of the wildtype group and 55.6% in the non-wild-type group (p = 0.891). The antitumor effects as assessed by response rate were 26.1% in the wildtype group and 55.6% in the non-wild-type group (p = 0.054). The median observation period was 13 months. The median progression-free survival was three months in the wild-type group vs. five months in non-wild-type group (p = 0.913), while the median overall survival was 24 vs. 22 months (p = 0.535). Conclusions: This study did not demonstrate a statistically significant difference in the usefulness of CPT-11 + PLD combination therapy for recurrent ovarian cancer between the two groups of UGT1A1 genotypes. This study was considered to have significance as the first study conducted in Japan to prospectively evaluate the relationship between the usefulness of CPT-11-based chemotherapy and the UGT1A1 genotype for recurrent ovarian cancer.

Key words: Recurrent ovarian cancer; Chemotherapy; CPT-11; PLD; UGT1A1.

Introduction

Many drug-metabolizing enzymes and drug transporters are involved in the disposition of irinotecan hydrochloride (CPT-11). Uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1), a drug-metabolizing enzyme, draws much attention because of its association with the occurrence of adverse drug reactions. According to a report by Ando et al., UGT1A1*28, a UGT1A1 polymorphism, was associated with the occurrence of severe adverse drug reactions to CPT-11 [1]. Many additional studies have since been conducted in Europe and the United States, suggesting the importance of the UGT1A1*28 polymorphism [2-5]. Moreover, the UGT1A1*6 polymorphism is present in 15% to 25% of the East Asian population. Currently, severe adverse drug reactions to CPT-11 have been increasingly reported in Japanese individuals with the UGT1A1*6 polymorphism as well as those with the UGT1A1*28 polymorphism [6, 7].

The tumor response and adverse events after chemotherapy with CPT-11, although widely known to be useful for recurrent ovarian cancer [8-10], may differ in each case and thus are difficult to predict. Severe adverse drug reactions to CPT-11 are considered highly likely to occur in patients with polymorphisms of the UGT1A1 gene encoding uridine diphosphate-glucuronosyl transferase, which is a major CPT-11-metabolizing enzyme. However, there is no definite conclusion about the antitumor effect of CPT-11 in ovarian cancer patients with UGT1A1 polymorphisms. Therefore, the authors evaluated the correlations between UGT1A1 polymorphisms and the efficacy of chemotherapy with CPT-11 as well as adverse events according to protocol.

Materials and Methods

This study protocol was reviewed and approved by the independent ethics committee or the institutional review
Relationship between usefulness of irinotecan and pegylated liposomal doxorubicin therapy...

Table 1. — Patients Characteristics

| Wild type (n = 23) | Non-Wild type (n = 18) | p value |
|-------------------|----------------------|---------|
| Age (median,range) | 57 (38-74)           | 55 (41-70) | 0.519** |
| PS                |                      |          | 0.338*  |
| 0                 | 20                   | 14       |         |
| 1                 | 3                    | 4        |         |
| Cell type         |                      |          | 0.815*  |
| Serous            | 18                   | 14       |         |
| Mucinus           | 1                    | 0        |         |
| Clear             | 4                    | 3        |         |
| Endometrioid      | 0                    | 1        |         |
| Prior regimens (median) |              |          | 0.252*  |
| 1                 | 7                    | 10       |         |
| 2                 | 8                    | 6        |         |
| 3 <               | 3                    | 7        |         |
| TFI               |                      |          | 0.355*  |
| 3 < , < 6        | 9                    | 10       |         |
| 3                | 14                   | 8        |         |
| Cycle number (median,range) |              |          | 0.957** |
| Pelvic cavity     | 2                    | 2        |         |
| Peritoneum        | 13                   | 9        |         |
| Lymph nodes       | 8                    | 8        |         |
| Liver             | 2                    | 0        |         |
| Spleen            | 1                    | 0        |         |
| Lung              | 2                    | 1        |         |

*Fisher’s exact test
**Wilcoxon rank sum test

board of each participating institution, and the study was conducted according to the Declaration of Helsinki and local ethical and legal requirements. All patients gave written and informed consent to participate before the enrollment. This study included 41 patients who had received CPT-11 / pegylated liposomal doxorubicin (PLD) combination therapy for platinum-resistant recurrent ovarian cancer in the TGCU104 study conducted at Tohoku Gynecologic Cancer Unit (TGCU) between April 2010 and March 2015 and who provided informed consent for inclusion in the study of UGT1A1 polymorphisms.

Upon receiving approval from the intramural ethics committee of each study center, a multi-center clinical study was conducted in patients with recurrent ovarian cancer who met the following criteria and were enrolled in the study: (1) ovarian cancer confirmed by histological or cytological diagnosis, (2) recurrence less than six months after previous chemotherapy, (3) containing a measurable or evaluable lesion (including CA-125 level), (4) ECOG performance status (PS) 0 to 2, (5) 20 to 75-years-old, (6) expected survival time of at least two months, (7) major organs remained functional (white blood cell count ≥ 3,000/mm³, neutrophil count ≥ 1,500/mm³, platelet count ≥ 10,000/mm³, total bilirubin ≤ 1.5 mg/dL), and (8) informed consent provided. Exclusion criteria were (1) serious complication(s), (2) evident pulmonary fibrosis or interstitial pneumonitis, (3) pleural or cardiac effusion necessitating prompt local treatment, (4) brain metastasis requiring prompt treatment, (5) diarrhea (watery stool), (6) intestinal paralysis or intestinal obstruction, (7) active infection requiring treatment with antimicrobial agents, and (8) patients considered inappropriate as subjects by the physician in charge for any other reason.

UGT1A1 polymorphisms included in the analysis were classified into 3 groups: wild type (*1/*1), hetero type (*6 heterozygote [*1/*6] or *28 heterozygote [*1/*28]), and homo type (*6 homozygote [*1/*6], *28 homozygote [*28/*28], or compound heterozygotes [*6/*28]).

According to a phase I study, CPT-11 was administered intravenously at a dose of 80 mg/m² on days 1 and 15. PLD
Progression-free survival. Progression-free survival. The median PFS was 3 months (range, 2-45 months) for the wild-type group, and 5 months (2-94 months) for the non-wild-type group. There was no statistically significant difference (hazard ratios [HR]: 0.99, 95% confidence interval [CI]: 0.52-1.95, \( p = 0.913 \)) between the wild-type and non-wild-type groups.

Overall survival. Overall survival. The median OS was 24 months (range, 2-64 months), for the wild-type group, and 22 months (range 2-94 months) for the non-wild-type group. There was no statistically significant difference (HR: 1.15, 95% CI: 0.45-3.14, \( p = 0.535 \)) between the wild-type and non-wild-type groups.

was administered intravenously at a dose of 30 mg/m\(^2\) on day 3 [9]. One course of chemotherapy was 28 days and, patients were given at least two courses, until PD.

If any of the following applied, CPT-11 administration on day 15 was to be postponed and the drug was to be administered on day 22 upon confirming recovery from the condition: (1) white blood cell count \( \leq 2,000/\text{mm}^3 \), (2) neutrophil count \( \leq 1,000/\text{mm}^3 \), (3) platelet count \( \leq 75,000/\text{mm}^3 \), or (4) grade 1 or higher diarrhea. If recovery from the condition was not seen on day 22, the second CPT-11 administration was to be skipped (not to be administered on day 29). The criteria for proceeding to the second and subsequent courses were (1) white blood cell count \( \geq 3,000/\text{mm}^3 \), (2) neutrophil count \( \geq 1,500/\text{mm}^3 \), (3) platelet count \( \geq 100,000/\text{mm}^3 \), (4) total bilirubin \( \leq 1.5 \text{mg/dL} \), (5) diarrhea grade 0, and (6) grade 1 or lower hand foot syndrome and mucositis. If the patient met any of the above criteria, administration was to be performed after waiting for recovery for a maximum of 14 days. If recovery from these conditions was not seen after 14 days, the treatment was discontinued. If the severity of hand foot syndrome or mucositis remained at grade 2 or higher after a 14-day postponement, PLD on day 3 in the next course was skipped.

The doses of CPT-11 and PLD in the next course were reduced according to the severity of adverse reactions that occurred in the previous course. If grade 4 leukopenia, grade 4 neutropenia, or grade 3 thrombocytopenia were observed in the previous course, CPT-11 was reduced by 10 mg/m\(^2\), and PLD by 7.5 mg/m\(^2\). If grade 2 or higher diarrhea, spasmodic abdominal pain, or watery stool was observed, the CPT-11 dose was reduced by 10 mg/m\(^2\). If grade 3 hand foot syndrome or mucositis was observed, the PLD dose was reduced by 7.5 mg/m\(^2\) regardless of whether or not these conditions improved before the start of the next course.

The antitumor effect was evaluated by imaging at the end of every two courses. For evaluation of the antitumor effect, the best response rate was calculated according to the RECIST (Response Evaluation Criteria in Solid Tumors) version1.0 Guideline. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) version 4.0.

Patients studied were divided into the following two groups according to \( UGT1A1 \) genotypes: wild type and non-wild type (hetero type and homo type). The adverse events, antitumor effect, and outcome of CPT-11/PLD combination therapy were compared between the two groups.

The Wilcoxon rank sum test, chi-square test and Fisher’s exact test were used to compare the patient characteristics, adverse events, and antitumor effect between the \( UGT1A1 \) wild-type and \( UGT1A1 \) non-wild-type groups.

Progression-free survival and overall survival were calculated from the date of start of chemotherapy, to the documented date of progression, death or last follow-up, whichever occurred first. Impact of chemotherapy result on survival was assessed by constructing Kaplan-Meier curves with a log-rank test. Coxregression analyses were performed to assess the prognostic factors on survival. All reported significance was two-tailed at a level of 0.05.

Results

Among the 41 patients, 23 (56.1%) were wild type, 16 (39.0%) were hetero type, and 2 (4.9%) were homo type for \( UGT1A1 \). Among the 16 hetero-type patients, 13 (81.3%) were heterozygote (*1/*6), and 3 (18.8%) were heterozygote (*1/*28). The 2 homo-type patients were both com-
pound heterozygotes (*6/*28). Comparison of the patient characteristics between the wild-type group (n = 23) and the non-wild-type group (n = 18) showed no statistically significant difference in age, performance status, cell type, prior regimens, number of treatment cycles, or recurrence site. The proportion of patients with a treatment free interval (TFI) of < 3 months was higher in the wild-type group (14/23, 60.9%) than in the non-wild-type group and that of patients with a TFI of 3-6 months was higher in the non-wild-type group (10/18, 55.6%) than in the wild-type group, although without statistically significant differences (p = 0.21) (Table 1). There was no significant difference in the occurrence of grade 3 or higher adverse events between the wild-type and non-wild-type groups (Table 2).

In a total of 94 treatment cycles given in the wild-type group (n = 23), the beginning of the next treatment cycle was postponed in nine cycles (9.6%). The reasons for postponement was the occurrence of adverse events, including neutrophil count < 1,500/mm^3. CPT-11 on day 15 was skipped in two cycles (2.1%) due to platelet count < 75,000/mm^3. On the other hand, of a total of 73 treatment cycles given in the non-wild-type group (n = 18), the beginning of the next treatment cycle was postponed due to occurrence of adverse events in ten cycles (13.7%). The reasons for postponement included neutrophil count of < 1500/mm^3 in nine (12.3%) cycles and the occurrence of hand-foot syndrome in one cycle. CPT-11 on Day 15 was postponed in one (1.4%) cycle because of the occurrence of intestinal obstruction.

The doses of CPT-11 and PLD in the next cycle were reduced only in one wild-type patient due to the occurrence of grade 4 neutropenia. The proportion of patients in whom the next cycle was postponed due to neutrophil count of < 1,500/mm^3 tended to be higher in the non-wild-type group (12.3%) than in the wild-type group (9.6%) (p = 0.891).

Evaluation of the antitumor effects of CPT-11 + PLD combination therapy showed that in the wild-type group (n = 23), partial response (PR), stable disease (SD), and progressive disease (PD) were observed in 6, 7, and 10 patients, respectively, with a response rate of 26.1%, while in the non-wild-type group (n = 18), PR, SD, and PD were observed in 10, 5, and 3 patients, with a response rate of 55.6% (p = 0.054). The disease control rate was 56.5% in the wild-type group and 83.1% in the non-wild-type group (p = 0.067) (Table 3).

The median observation period was 13 (range, 6-94) months. The median progression-free survival (PFS) and overall survival (OS) were 3 (range, 2-45) months and 24 (range 2-64) months, respectively, for the wild-type group, and 5 (range 2-94) months and 22 (range 2-94) months for the non-wild-type group. The Kaplan-Meier curve with a log-rank test showed no statistically significant difference in PFS [hazard ratios (HR): 0.99, 95% confidence interval (CI): 0.52-1.95, p = 0.913] or OS (HR: 1.15, 95% CI: 0.45-3.14, p = 0.535) between the wild-type and non-wild-type groups (Figures 1 and 2).

### Table 2. — Adverse effects (n = 41, > Grade 3)

|          | Wild type (n = 23) | Non-Wild type (n = 18) | p value |
|----------|-------------------|------------------------|---------|
| Leucopenia | 0.353             | 0.261                  | 0.5299  |
| Neutropenia | 0.529             | 0.522                  | 0.9617  |
| Anemia    | 0.118             | 0.043                  | 0.3876  |
| Thrombocytopenia | 0.059    | 0.043                  | 0.8258  |
| Mucositis | 0                 | 0                      | -       |
| Hand foot | 0                 | 0                      | -       |
| Diarrhea  | 0                 | 0.118                  | 0.0915  |
| Nausea    | 0.059             | 0                      | 0.2388  |
| Vomiting  | 0.118             | 0.043                  | 0.3786  |
| Appetite loss | 0        | 0                      | -       |
| Fatigue   | 0                 | 0.043                  | 0.3839  |

### Table 3. — Tumor Response (n = 41)

|          | Wild type | Non-Wild type | Total | p value |
|----------|-----------|---------------|-------|---------|
| CR       | 0         | 0             | 0     |         |
| PR       | 6         | 10            | 16    |         |
| SD       | 7         | 5             | 12    |         |
| PD       | 10        | 3             | 13    |         |
| Overall response (%) | 6 (26.1%) | 10 (55.6%) | 16 (39.0%) | 0.054 |
| CR/PR + SD (%) | 13 (56.5%) | 15 (83.3%) | 28 (68.3%) | 0.067 |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

### Discussion

This study was conducted as an additional study of a phase II clinical trial (TGCU104 study). Several reports have suggested that the risk of toxicities increases more in the hetero-/homo-group patients than in patients harboring the wild-type genotype [1, 6, 11, 12]. Each of the adverse events evaluated in this study showed no statistically significant difference between the wild-type UGT1A1 genotype and non-wild-type UGT1A1 genotype groups. However, grade 3 or higher diarrhea was observed in 11% of the non-wild-type group but not in the wild-type group. Although this study predominantly included patients initiating CPT-11 + PLD combination therapy shortly after or immediately following completion of the previous treatment regimen, hematologic toxicities were manageable, suggesting that the CPT-11 + PLD combination therapy has high patient compliance.

Takeo et al. reported low-dose irinotecan/platinum chemotherapy to be associated with increased risk of severe hematologic toxicity in UGT1A1 homo-type patients [13]. Yoshino et al. confirmed that irinotecan/gemcitabine (irinotecan 80-100 mg/m^2, gemcitabine 800-1000mg/m^2, day 1, 8 q 21 days) for platinum-resistant recurrent ovarian cancer resulted in grade 3/4 neutropenia in 100% of
In this study, two reasons were considered for this inconsistency. First, no platinum agents were used for the chemotherapy regimen in this study. Second, for the purpose of preventing the risk of occurrence of severe diarrhea and hematologic toxicity, the CPT-11 dose was given in two divided doses on days 1 and 15 of each cycle, and the criteria for administration and skipping of CPT-11 on day 15 and the criteria for starting the next treatment cycle were strictly determined. Two treatment cycles were postponed in wild-type patients, because their neutrophil counts did not meet the criteria for administration of CPT-11 on day 15. In addition, three and nine treatment cycles were postponed in wild-type and non-wild-type patients, respectively, because their neutrophil counts did not meet the criteria for starting the next treatment cycle. Protocol-based postponement of the administration of CPT-11 was considered to allow the prevention of the occurrence of severe hematologic toxicity.

Evaluation of the antitumor effect of the treatment showed that the response rate and disease control rate were 26.1% and 55.6%, respectively, in the wild-type group and 55.6% and 83.3%, respectively, in the non-wild-type group. The response rate tended to be higher, although without statistical significance, in the non-wild-type group. There is no definitive conclusion that UGT1A1 non-wild-type patients can achieve a good response rate in the field of ovarian cancer. Our results suggested that a good response rate could be achieved in UGT1A1 non-wild-type patients by increasing sample size; there were 41 in this study.

There was no statistically significant difference in PFS or OS between the wild-type and non-wild-type groups. This observation is considered to be presumable, as this chemotherapy using CPT-11 and PLD targeted patients with platinum-resistant recurrent ovarian cancer, in whom early postchemotherapy events are likely to occur.

Conclusions

This study did not demonstrate a statistically significant difference between the usefulness of CPT-11 + PLD combination therapy for recurrent ovarian cancer and the UGT1A1 genotype. However, the regimen defined to CPT-11 given in two divided doses on days 1 and 15 during each treatment course, and the criteria for beginning the next treatment course and the criteria for dose reduction in the next course were strictly determined. These efforts raised the possibility of safe and feasible CPT-11 + PLD combination therapy for recurrent ovarian cancer regardless of the patient’s UGT1A1 genotype.

This study was considered to have significance as the first study conducted in Japan that prospectively evaluated the relationship between the usefulness of CPT-11-based chemotherapy and the UGT1A1 genotype for recurrent ovarian cancer.

Authors’ contributions

T.Sh. contributed to the design and coordination of the study, and drafting the manuscript. T.Su. contributed to the design of the study and drafting the manuscript. E.T., M.K., M.F., Y.Y., H.T., N.Y., T.O. and T.W. contributed to the conception, design, and coordination of the study and drafting the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee (Institutional Review Board) of each study center (No. H22-9). It was conducted according to the Declaration of Helsinki for medical research. Written informed consent was obtained from all study participants.

Acknowledgements

The authors thank Yu Sakata (Misawa City Hospital), Junzo Kigawa (Matsue City Hospital), Masahiro Kashiwabara (Sagara Hospital) for advice on this research and the participating members of Tohoku Gynecologic Cancer Unit for clinical support of this study.

Conflict of interest

None of the authors of this manuscript has any conflicts of interest to declare.

Submitted: February 06, 2019
Accepted: July 16, 2019
Published: June 15, 2020

References

[1] Ando Y., Saka H., Ando M., Sugira S., Shimokata K., Kamatani T.: “Polymorphisms of UDP glucuronosyltransferase gene and irinotecan toxicity: A pharmacogenetic analysis”. Cancer Res., 2000, 60, 6921.
[2] Iyer L., Das S., Janisch L., Wen M., Ramirez J., Harrison T., et al.: “UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity”. Pharmacogenomics J., 2002, 2, 43.
[3] Innocenti F., Undevia S.D., Iyer L., Chen P.X., Das S., Kocherginsky M., et al.: “Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan”. J. Clin. Oncol., 2004, 22, 1382.
[4] Marcuello E., Alés A., Menoyo A., Del Rio E., Gómez-Pardo M., Baiget M.: “UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer”. Br. J. Cancer, 2004, 91, 678.
[5] Rouits E., Boisdon-Celle M., Dumont A., Guérian O., Morel A., Gamelin E.: “Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity: a molecular and clinical study of 75 patients”. Clin. Cancer Res., 2004, 10, 5151.
[6] Minami H., Sai K., Saeki M., Saito Y., Ozawa S., Suzuki K., et al.: “Irinotecan pharmacokinetics / pharmacodynamics and UGT1A1 genetic polymorphisms in Japanese: roles of UGT1A1*6 and *28”. Pharmacogenet Genomics, 2007, 17, 497.
[7] Takatori E., Shoji T., Miura Y., Takeuchi S., Yoshizaki A., Sugiyama T.: “Recurrent cervical cancer in a patient who was compound heterozygous for UGT1A1*6 and UGT1A1*28 presenting with serious adverse events during irinotecan hydrochloride/nedaplatin therapy”. J. Obstet. Gynaecol. Res., 2013, 39, 1354.
[8] Shoji T., Takatori E., Omi H., Kumanagi S., Yoshizaki A., Yokoyama Y., et al.: “Phase II clinical study of the combination chemotherapy regimen of irinotecan plus oral etoposide for the treatment of recur-
rent ovarian cancer (Tohoku Gynecologic Cancer Unit 101 Group Study)”. *Int. J. Gynecol. Cancer*, 2011, 21, 44.
[9] Shoji T., Takatori E., Kaido Y., Omi H., Yokoyama Y., Mizunuma H., *et al.*: “A phase I study of irinotecan and pegylated liposomal doxorubicin in recurrent ovarian cancer (Tohoku Gynecologic Cancer Unit 104 study)”. *Cancer Chemother. Pharmacol.*, 2014, 73, 895.
[10] Matsumoto K., Katsumata N., Yamanaka Y., Yonemori K., Kohno T., Shimizu C., *et al.*: “The safety and efficacy of the weekly dosing of irinotecan for platinum- and taxanes-resistant epithelial ovarian cancer”. *Gynecol. Oncol.*, 2006, 100, 412.
[11] Takano M., Kato M., Yoshikawa T., Sasaki N., Hirata J., Furuya K., *et al.*: “Clinical significance of UDP-glucuronosyltransferase 1A1*6 for toxicities of combination chemotherapy with irinotecan and cisplatin in gynecologic cancers: A prospective multi-institutional study”. *Oncology*, 2009, 76, 315.
[12] Chen Y.J., Hu F., Li C.Y., Fang J.M., Chu L., Zhang X., *et al.*: “The association of UGT1A1*6 and UGT1A1*28 with irinotecan-induced neutropenia in Asians: a meta-analysis”. *Biomarkers*, 2014, 19, 56.
[13] Takano M., Yamamoto K., Tabata T., Minegishi Y., Yokoyama T., Hirata E., *et al.*: “Impact of UGT1A1 genotype upon toxicities of combination with low-dose irinotecan plus platinum”. *Asia Pac. J. Clin. Oncol.*, 2016, 12, 115.
[14] Yoshino K., Kamiura S., Yokoi T., Nakae R., Fujita M., Takemura M., *et al.*: “Combination chemotherapy with irinotecan and gemcitabine for taxane/platinum-resistant/refractory ovarian and primary peritoneal cancer: a multicenter phase I/II trial (GOGO-Ov 6)”. *Cancer Chemother. Pharmacol.*, 2017, 80, 1239.

Corresponding Author:
Tadahiro Shoji, M.D., Ph.D.
Department of Obstetrics and Gynecology,
Iwate Medical University School of Medicine,
19-1 Uchimaru, Morioka 020-8505 (Japan)
E-mail: tshoji@iwate-med.ac.jp