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Original Article

Tailored-dose chemotherapy with gemcitabine and irinotecan in patients with platinum-refractory/resistant ovarian or primary peritoneal cancer: a phase II trial

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ABSTRACT

Objective: We investigated the efficacy and toxicity of tailored-dose chemotherapy with gemcitabine and irinotecan for platinum-refractory/resistant ovarian or primary peritoneal cancer.
Methods: We enrolled patients with ovarian or primary peritoneal cancer who received ≥2 previous chemotherapeutic regimens but developed progressive disease during platinum-based chemotherapy or within 6 months post-treatment. All patients received gemcitabine (500 mg/m^2) and irinotecan (50 mg/m^2) on days 1 and 8 every 21 days at the starting dose. The dose was increased or decreased by 4 levels in subsequent cycles based on hematological or non-hematological toxicities observed. The primary endpoint was progression-free survival (PFS), and secondary endpoints were disease control rate (DCR), overall survival (OS), and adverse events.
Results: We investigated 25 patients who received 267 cycles (median 8 cycles/patient) between October 2008 and May 2011. Tailored-dose gemcitabine was administered up to the 5th cycle as follows: 1,000 mg/m^2 in 1 (4%), 750 mg/m^2 in 16 (64%), 500 mg/m^2 in 6 (24%), and 250 mg/m^2 in 2 patients (8%). The median PFS and OS were 6.2 months (95% confidence interval [CI]=2.7–10.7) and 16.8 months (95% CI=9.4–30.7), respectively. The DCR was 76%, and PFS was >6 months in 12 of 25 patients (48%). Grade 3 hematological toxicities included leukopenia (9.4%), neutropenia (11.2%), anemia (9.8%), and thrombocytopenia (1.1%). Grade 3/4 non-hematological toxicities did not occur except for fatigue in one patient.
Conclusions: Tailored-dose chemotherapy with gemcitabine and irinotecan was effective and well tolerated in patients with platinum-refractory/resistant ovarian or primary peritoneal cancer.

Trial Registration: UMIN Clinical Trials Registry Identifier: UMIN000004449

Keywords: Chemotherapy; Gemcitabine; Drug Toxicity; Irinotecan; Ovarian Cancer; Recurrence

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

Author Contributions
Conceptualization: T.S., T.Y., M.S.; Data curation: T.S.; Formal analysis: T.S.; Funding acquisition: T.S.; Investigation: T.S., N.K., M.A., O.S., K.K.; Methodology: T.S., T.Y.; Visualization: T.S.; Writing - original draft: T.S., N.K., M.A., O.S., K.K., T.Y., M.S.; Writing - review & editing: T.S., N.K., M.A., O.S., K.K., T.Y., M.S.

INTRODUCTION

Several phase III trials have recommended single-agent over combination chemotherapy as salvage chemotherapy for platinum-refractory/resistant ovarian cancer because combination chemotherapy was not shown to prolong survival and was associated with greater treatment-induced toxicities [1-5]. Usually, the recommended chemotherapeutic dose is determined by the maximum tolerated dose (MTD) based on dose-limiting toxicities observed in the study population. However, the recommended dose determined by the MTD could cause major adverse events and reduce patient compliance with salvage chemotherapy. Bone marrow function differs across patients who receive salvage chemotherapy and depends on the cumulative dose of previous chemotherapy and tumor load. Therefore, it is necessary to determine a tailored dose based on a patient's specific needs to ensure sustained salvage chemotherapy.

Tailored-dose chemotherapy enables dose modifications in subsequent cycles (increasing or decreasing the dose) based on the toxicities observed in patients and therefore facilitates continuation of chemotherapy [6-8]. In contrast to low-dose chemotherapy [9], tailored-dose chemotherapy enables dose escalation in patients without toxicities and may contribute to the therapeutic benefits of dose escalation. Therefore, tailored-dose chemotherapy minimizes the risk of toxicities and can ensure good patient compliance for sustained treatment, resulting in disease stabilization [10,11]. We expected that tailored-dose chemotherapy would effectively minimize unacceptable toxicities and improve patient compliance for long-term uninterrupted treatment.

Combination chemotherapy comprising several drug regimens such as paclitaxel+epirubicin [3], topotecan+gemcitabine or etoposide, weekly paclitaxel+triweekly carboplatin [4], and weekly paclitaxel+topotecan [5] is used as salvage chemotherapy for platinum-refractory/resistant ovarian cancer. However, previous clinical studies could not confirm the synergistic effects of combination chemotherapy with regard to survival benefit, although these regimens were associated with significant adverse effects. Irinotecan and gemcitabine are non-cross resistant to paclitaxel and platinum agents used as first-line chemotherapy. Additionally, in vitro studies have reported the synergistic effects of irinotecan and gemcitabine [12,13]. Some clinical studies have confirmed the efficacy and safety of combination chemotherapy using gemcitabine and irinotecan in patients with pancreatic [14] and lung cancer [15]. Previous reports have described combination chemotherapy using irinotecan and gemcitabine (at MTD-determined doses) for patients with platinum-resistant/refractory ovarian cancer [16]; however, no report has described tailored-dose chemotherapy with gemcitabine and irinotecan. Therefore, in this phase II trial, we investigated the efficacy of tailored-dose chemotherapy with gemcitabine and irinotecan using an initial dose that was half the recommended MTD-determined dose for patients with recurrent/refractory ovarian and peritoneal cancers.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board (#2038) of Chiba University Hospital (UMIN ID: UMIN000004449). Informed consent was obtained from all patients enrolled in the trial.

1. Eligibility criteria

Following were the inclusion criteria for this study: age >20 years but <75 years, a documented histopathological diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, administration of ≥2 prior platinum-based chemotherapeutic regimens, progression of disease during the most recent platinum-based chemotherapy (platinum-refractory disease) or within 6 months of completing prior therapy (platinum-resistant disease), measurable disease with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score 0–2, adequate bone marrow reserve and hepatic and renal function, and no administration of monoclonal antibodies and small molecule inhibitors during the study period.

2. Exclusion criteria

Patients with any of the following conditions were excluded from the study: i) severe systemic or uncontrolled disease (uncontrolled diabetes mellitus or hypertension), ii) clinically unstable seizures requiring anticonvulsants, iii) gastric outlet or intestinal obstruction, iv) mental illness or dementia, and v) known hypersensitivity to gemcitabine and irinotecan. The use of either irinotecan or gemcitabine in the previous chemotherapy was not considered a non-eligibility criterion.

3. Treatment protocol

We administered tailored-dose gemcitabine via intravenous infusion over 30–60 minutes and tailored-dose irinotecan via intravenous infusion over 90 minutes on days 1 and 8 every 3 weeks. Patients did not receive prophylactic granulocyte colony-stimulating factor. Treatment continued until patients developed progressive disease or unacceptable toxicity.

4. Dose modification

Previous studies have reported that the dosage of gemcitabine and irinotecan recommended for non-gynecologic cancer was 1,000 mg/m^2 and 100 mg/m^2, respectively in phase I trials investigating untreated patients with advanced non-small cell lung cancer [15] and in a phase III trial investigating advanced or recurrent pancreatic cancer [14]. Each agent was administered on days 1 and 8 every 3 weeks. This dosage was the recommended dose defined by the MTD. Yoshino et al. [16] reported that gemcitabine 1,000 mg/m^2 and irinotecan 100 mg/m^2 determined by the MTD-method was the recommended dosage, but they reported that the incidence of grade 3/4 diarrhoea was 8.6%, while the incidence of grade 3/4 was high in neutropenia (60%) and anemia (17.1%). To reduce the incidence of hematological toxicity, we set the initial dose at half the recommended dose (gemcitabine 500 mg/m^2 and irinotecan 50 mg/m^2, dose level 0). Therefore, the dose of irinotecan was not reduced because it was unlikely that a dose reduction of 50 mg/m^2 or less of irinotecan would reduce the incidence of diarrhea. The dose modification schedule is shown in **Table 1**. The initial dosage was administered at dose level 0, and a reduced dose level was considered for the subsequent cycle in patients with hematological or non-hematological toxicities ≥grade 3. The dose level was

Table 1. Dose modification schedules

Level	Irinotecan (mg/m^2)	Gemcitabine (mg/m^2)
−2	50	100
−1	50	250
0	50	500
1	50	750
2	70	1,000
3	100	1,000

We set the initial dose of tailored-dose chemotherapy to half the recommended dose determined by the maximum tolerated dose (gemcitabine: 500 mg/m^2, irinotecan: 50 mg/m^2, dose level 0).

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increased during the subsequent cycle in patients in whom all toxicities (hematological and non-hematological) were classified as ≤grade 1; the drug dose was unchanged in the other categories. For example, the drug dose was unchanged during the subsequent cycle in patients in whom the hematological and non-hematological toxicities were categorized as grades 2 and 1, respectively. The doses of both gemcitabine and irinotecan were changed even when diarrhea was categorized as grade 3. Treatment was deferred and a maximum delay of one week was allowed in patients in whom these values were not observed on the day of drug administration.

5. Patient assessment

We assessed the adverse events on days 1 and 8 throughout the duration of drug administration. No patient required hospitalization when evaluated on day 15, particularly in the absence of symptoms. The Common Terminology Criteria for Adverse Events scale, version 3.0 issued by the National Cancer Institute was used to grade toxicity in all patients. Computed tomography was performed after every 2 cycles and tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumors, version 1.1. A complete response (CR) was defined as disappearance of all assessable target lesions without evidence of new lesions. Partial response (PR) was defined as at least 30% reduction in the sum of the longest diameter of all target lesions. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of all target lesions or development of new lesions. Stable disease (SD) was defined as any condition not meeting the aforementioned criteria. The disease control rate (DCR) was defined as either a tumor response (CR+PR) or SD [17].

6. Statistical analysis

This was a prospective, open, single-arm single-center trial. The sample size was calculated to ensure a power of 80% and a type 1 error of 5%. Reportedly, the median progression-free survival (PFS) for patients with platinum-refractory/resistant ovarian cancer was from 3 to 5 months [17]; therefore, we concluded that the estimated PFS was 5 months, and the threshold PFS was 3 months. The accrual time was set at 24 months, and the follow-up interval at 12 months. The target sample size required the inclusion of 23 patients; however, considering possible enrollment of ineligible patients, we enrolled 25 patients. The primary endpoint was PFS defined as the interval between study enrollment and progressive disease or death. The secondary endpoints were DCR, overall survival (OS), drug tolerability, and toxicity. OS was defined as the interval between study enrollment and death. The intention-to-treat population (which included all patients) was used for primary analysis. The Kaplan-Meier method was used to estimate PFS and OS curves for each treatment arm. The log-rank test was used for subgroup analysis to compare PFS. All data were analyzed based on the intention-to-treat principle. All tests were two-sided. A p-value <0.05 was considered statistically significant. All analyses were performed using the JMP software, version 11.0 (SAS, Cary, NC, USA).

RESULTS

1. Patient characteristics

We enrolled 25 patients between October 2008 and May 2011; 17 of these 25 patients were referred to Chiba University Hospital to participate in this study from affiliated hospitals. Patient characteristics are shown in **Table 2**. Median patient age was 60 years. The primary site of involvement was the ovary in 21 (84%) and the peritoneum in 4 patients (16%), and 17 of 25 patients (68%) showed an ECOG PS score of 0. High-grade serous carcinoma was observed in 19 patients (76%), and early stage (I/II) disease was identified in 5 (20%) and

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Table 2. Patient characteristics (n=25)

Characteristics	Values
Age (yr)	60 (51–68)
Primary site	
Ovary	21 (84.0)
Peritnium	4 (16.0)
PS	
0	17 (68.0)
1	8 (32.0)
2	0 (0.0)
Histology	
Serous carcinoma, high grade	19 (76.0)
Clear cell carcinoma	3 (12.0)
Endometrioid carcinoma	3 (12.0)
FIGO stage at primary diagnosis	
I/II	5 (20.0)
III/IV	18 (72.0)
Unknown	2 (8.0)
Baseline CA-125 (U/mL)	196 (32–953)
Previous chemotherapy regimen	
2	14 (56)
3	9 (36)
>4	2 (8)
PFI (mo)	3.5 (1.6–5.2)

Values are presented as median (IQR) or number (%).
CA, carbohydrate antigen; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; PFI, platinum-free interval; PS, performance status.

advanced stage (III/IV) disease in 18 patients (72%) at the time of diagnosis. Notably, 14 (56%) and 11 patients (44%) had previously received two and ≥3 chemotherapeutic regimens, respectively. The median serum cancer antigen 125 level at the time of study enrollment was 196 IU/mL. The median platinum-free interval (PFI) was 3.5 months (interquartile range [IQR], 1.6–5.2). The median follow-up period was 16.8 months, and all 25 patients died until March 2019 (maximum survival period 116 months).

2. Treatment administration

A total of 246 cycles were administered in this study. The median number of cycles administered per patient was 8 cycles (range 1–28 cycles). Dose modification up to the 5th cycle is shown in **Fig. 1**. Of the 25 patients who received the first cycle of chemotherapy,

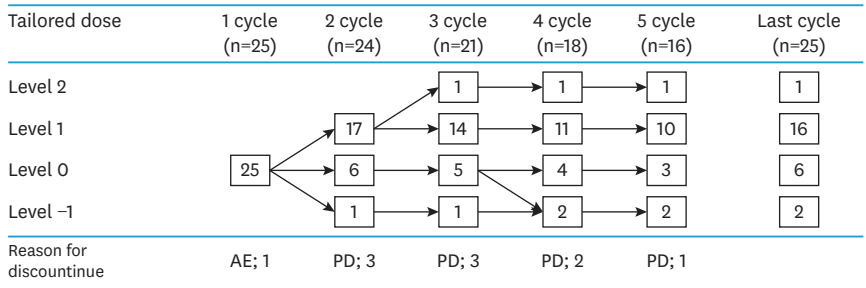

Fig. 1. Changes in dose levels of tailored-dose chemotherapy using gemcitabine and irinotecan up to the 5th cycle
Nine patients discontinued chemotherapy owing to PD and one patient owing to AE until the administration of the 5th cycle. The number of patients corresponding to each dose level at the time of administration of the 5th cycle (at the time of treatment discontinuation) is shown to the right in the figure. The number of patients who received treatment during the last cycle includes those who discontinued chemotherapy secondary to disease progression or adverse events.
AE, adverse effect; PD, progressive disease.

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one patient discontinued treatment owing to adverse effects. The second cycle was administered to 24 patients; the dose level was subsequently increased in 17 patients, reduced in one patient, and maintained at the same level in 6 patients. Three patients developed progressive disease and discontinued treatment during the second cycle. The third cycle was administered to 21 patients; 1 patient received dosage level 2, 14 received dosage level 1, 5 received dosage level 0, and one received dosage level –1. Three patients developed progressive disease during the third cycle. The fourth cycle was administered to 18 patients. The tailored dose administered up to the 5th cycle was level 2 in 1 (4%), level 1 in 16 (64%), level 0 in 6 (24%), and level –1 in 2 patients (8%). Therefore, we observed a 4-fold difference in the individual drug dosage of gemcitabine administered in this study.

3. Efficacy

The PFS was 6.2 months (95% confidence interval [CI]=2.7–10.7), and the OS was 16.8 months (95% CI=9.4–30.7) (**Fig. 2**). Among all 25 patients, the response rate was as follows: CR 1 (4%), PR 4 (16%), SD 14 (56%), and progressive disease in 6 patients (24%). Notably, the DCR was 19 (76%), and 12 patients (48%) showed PFS >6 months (**Fig. 3**). PFS was associated with the PFI ($p<0.001$) but not with drug response (**Supplementary Fig. 1**).

4. Toxicity

We administered a total of 276 cycles to 25 patients in this study. The adverse effects were analyzed for a total of 246 cycles because the tailored dose was adjusted in subsequent cycles based on patients' toxicities (**Table 3**). Grade 3 hematological toxicities included leukopenia (9.4%), neutropenia (11.2%), anemia (9.8%), and thrombocytopenia (1.1%). Grade 4 hematological toxicity and febrile neutropenia (FN) did not occur. Among non-hematological toxicities (grade 3/4), fatigue was observed in 4% of patients; however, no grade 3/4 toxicities were observed. Peripheral neuropathy was the most common grade 2 adverse effect, although paclitaxel had been administered before the last chemotherapy cycle in many of these patients. No adverse event-induced mortality was observed. A woman developed edematous erythema mainly on the trunk on the fourth day of administration of the first cycle. However, she improved with external application of steroids and systemic administration of prednisone (15 mg) and discontinued chemotherapy owing to the drug eruption.

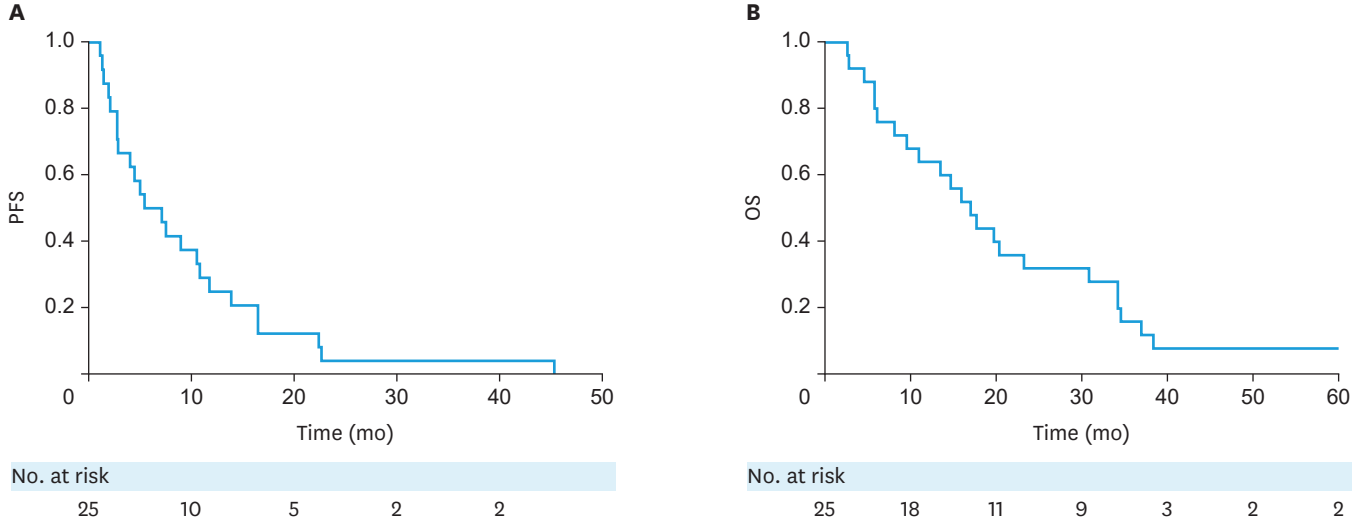

Fig. 2. (A) PFS and (B) OS.
OS, overall survival; PFS, progression-free survival.

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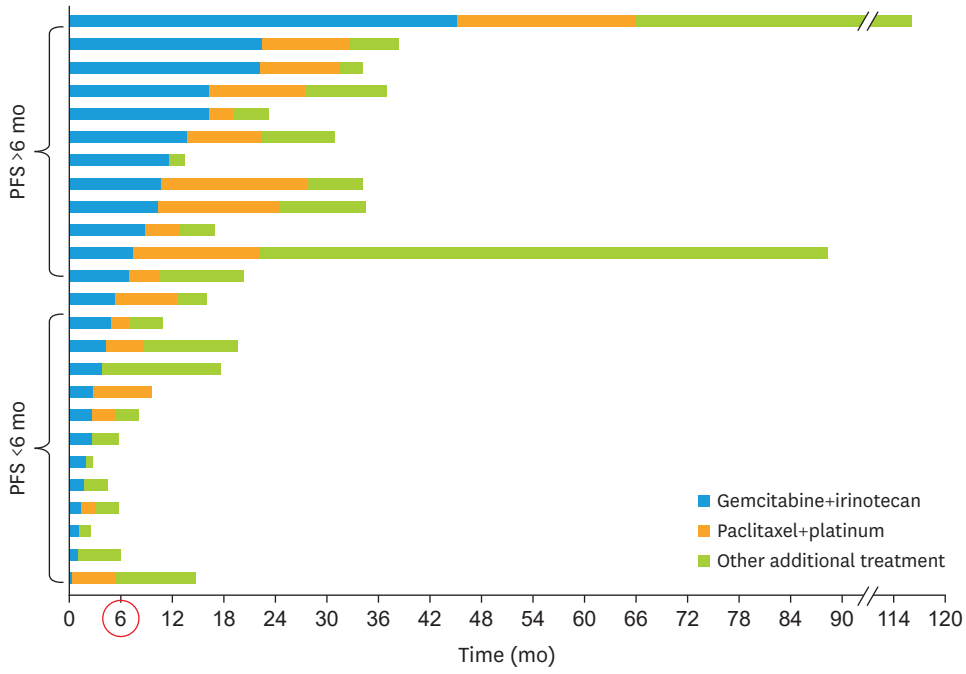

Fig. 3. Survival post progression. The blue line represents the period during which patients received tailored-dose chemotherapy with gemcitabine and irinotecan. The orange line represents the period during which patients received combination chemotherapy with paclitaxel and platinum. The light green line represents the period during which patients received other chemotherapy or palliative care. All 25 patients died until March 2019 (survival period 116 months).
PFS, progression-free survival.

Table 3. Adverse events considered once per cycle (cycle=276)

Adverse event term	CTCAE grade		
	2	3	4
Nonhematologic			
Fatigue	5 (1.8)	1 (0.4)	0 (0.0)
Anorexia	17 (6.2)	0 (0.0)	0 (0.0)
Nausea/Vomiting	14 (5.1)	0 (0.0)	0 (0.0)
Constipation	7 (2.5)	0 (0.0)	0 (0.0)
Diarrhea	8 (2.9)	0 (0.0)	0 (0.0)
Dyspnea	17 (6.2)	0 (0.0)	0 (0.0)
Peripheral neuropathy	28 (10.1)	0 (0.0)	0 (0.0)
Arthralgia/Myalgia	4 (1.4)	0 (0.0)	0 (0.0)
Hand-foot syndrome	8 (2.9)	0 (0.0)	0 (0.0)
Mucositis	0 (0.0)	0 (0.0)	0 (0.0)
Hematologic			
Leucopenia	90 (32.6)	26 (9.4)	0 (0.0)
Neutropenia	67 (24.3)	31 (11.2)	0 (0.0)
Anemia	92 (33.3)	27 (9.8)	0 (0.0)
Thrombocytopenia	4 (1.4)	3 (1.1)	0 (0.0)

Values are presented as number (%).
CTCAE, Common Terminology Criteria for Adverse Events.

5. Subgroup analysis

Patients' age and the number of previous chemotherapeutic regimens were not prognostic indicators of PFS or OS; however, the ECOG PS score was a significant prognostic indicator of PFS and OS. No significant differences were observed in survival times (represented by PFS and OS rates) between the different dosage groups (**Supplementary Fig. 2**). Evaluation of the effect of stabilization on OS revealed that compared with patients showing PFS <6 months

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(13/25, 52%), patients with PFS >6 months (12/25 patients, 48%) showed significantly longer OS (**Supplementary Fig. 3**). No significant association was observed between PFS ≥6 months and the drug dosage level (p=0.688).

6. Post-progression survival

We exploratively evaluated treatment received after study completion. Compared with patients showing PFS <6 months, a greater number of patients showing PFS >6 months received paclitaxel plus platinum chemotherapy after protocol discontinuation (7 of 13 patients [54%] vs. 11 of 12 patients [92%], p=0.073) (**Fig. 3**). Patients who received paclitaxel-platinum combination chemotherapy after completion of this study protocol received combination chemotherapy with gemcitabine and irinotecan for a median of 14 cycles (IQR, 9.5–20), whereas patients who received pegylated liposomal doxorubicin (n=4) or palliative treatment (n=7) after completion of the study protocol were administered this regimen for a median of 3 cycles (IQR, 2–5). We observed a significant difference in the gemcitabine and irinotecan chemotherapy cycles between patients who did and did not receive paclitaxel-platinum (p<0.001).

7. The response rate and survival outcome for each histological type

The response rates and DCRs for each histological type were as follows: serous carcinoma (19 patients, CR 1, PR 3, SD 10, PD 5, and DCR 73.4%); endometrioid carcinoma (3 patients, CR 0, PR 1, SD 2, PD 0, DCR 100%); clear cell carcinoma (3 patients, CR 0, PR 0, SD 2, PD 1, DCR 66.7%).

The PFS and OS for each histological type were as follows: serous carcinoma (PFS 8.0 months, 95% confidence interval=2.8–11.7 and OS 17.6 months, 95% CI=9.4–30.7); clear cell carcinoma (PFS 2.0 months, 95% CI=1.9–5.3 and OS 4.4 months, 95% CI=2.6–15.7); endometrioid carcinoma (PFS 7.4 months, 95% CI=2.7–22.3 and OS 34.1 months, 95% CI=5.6–88.2).

DISCUSSION

This study showed that tailored-dose chemotherapy with gemcitabine and irinotecan was effective and safe in patients with platinum-refractory/resistant ovarian and peritoneal cancers. The DCR was 76%, and 48% of patients enrolled in this study showed PFS >6 months. Furthermore, grade 4 hematological toxicities and FN did not occur, and grade 3 hematological toxicities occurred in only approximately 10% of patients. These results could be attributed to the following factors: i) We used tailored drug doses in this study as opposed to the commonly used MTD. ii) Gemcitabine and irinotecan do not show cross-resistance with paclitaxel and carboplatin used as first-line chemotherapy. iii) Despite the use of combination chemotherapy, the reduced dose of each drug included in this regimen resulted in lower drug toxicities in this study. Tailored-dose chemotherapy with gemcitabine and irinotecan led to a high DCR and longer disease stabilization [10,11,17]. The extended PFI that was observed with the use of this protocol may have further prolonged OS by the re-administration of platinum-paclitaxel combination therapy after study completion.

The optimal drug dosage for salvage chemotherapy remains unclear. The conventional drug dosage used for salvage chemotherapy is determined by the MTD based on dose-limiting toxicities observed in the study population (similar to the protocol followed for

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first-line chemotherapy). Although doses of anticancer agents are adjusted based on body surface area, patients show wide differences in drug response or adverse effects owing to marked differences in the activity of metabolic enzymes, which is attributable to genetic polymorphisms [6,18]. We observe that despite the administration of a "specific dosage of anticancer agents" of MTD-determined chemotherapy, some patients showed "a poorer response or a higher rate of adverse effects" in daily practice. We also observe that efficacy is not necessarily dose-dependent. The efficacy of pegylated liposomal doxorubicin for recurrent ovarian cancer did not differ between 40 and 50 mg/m^2, but the risk of adverse events was reduced with 40 mg/m^2 [19]. In contrast to MTD-determined chemotherapy, tailored-dose therapy includes an increased or decreased dose based on patients' toxicities. Therefore, administration of a tailored dosage regimen based on evaluation of patients' toxicities can achieve a "predictable drug response and adverse effects," to minimize unacceptable toxicities and improve patient compliance with sustained therapy [7,8].

Unlike low-dose chemotherapy [9], tailored-dose chemotherapy involves several dose adjustments based on patients' toxicities; the tailored dose can be increased in patients with low-grade toxicities. After dose modification (based on reported toxicity), the tailored dose was gemcitabine 750 mg/m^2 and irinotecan 50 mg/m^2 (defined as dose level 1) in 64% of patients. We observed a 4-fold difference in the drug doses of gemcitabine administered in this study (level –1: 250 mg/m^2, level 2: 1,000 mg/m^2). This explains the high DCR and prolonged PFS associated with tailored-dose chemotherapy. In contrast to our study, Yoshino et al. reported combination therapy using gemcitabine and irinotecan for platinum resistant/refractory ovarian and peritoneal cancer in patients in whom the drug dosage was determined by the MTD [16]. Although patients' backgrounds were the same between the two studies, compared with the MTD-determined dosage in the previous study, our tailored-dose chemotherapy led to better PFS and lower rates of adverse events. We were concerned that the low-dose group might show a lower survival rate than the high-dose group because of the potential for undertreatment. We observed comparable survival outcomes between the low- and high-dose groups in this study. Owing to significant differences in patients' bone marrow activity and drug metabolism, a tailored dose was necessary for each patient to achieve the same survival outcome. These findings indicate that in addition to reducing the risks, tailored-dose chemotherapy is useful to optimize individualized chemotherapeutic dosing.

Single-agent chemotherapy is recommended in salvage settings to maintain patients' quality of life because compared with combination chemotherapy, single-agent chemotherapy is associated with a lower rate of adverse events [1-5]. However, in this study, we observed that tailored-dose combination chemotherapy was not associated with severe adverse effects. This observation could be attributed to the fact that the agents used in this study show different toxicity profiles, and the initial dose of these chemotherapeutic agents was set to half the recommended dose defined by the MTD for first-line chemotherapy. The tailored-dose approach led to lower rates of severe hematological toxicities (a known adverse effect of gemcitabine) and also reduced severity of diarrhea (a known adverse effect of irinotecan) [20].

Selection of gemcitabine and irinotecan in this study was guided by the following factors: i) We chose agents other than paclitaxel and carboplatin, which are usually administered as first-line chemotherapy. ii) Single-agent administration of gemcitabine or irinotecan have been shown to be effective for recurrent ovarian cancer [21,22]. iii) In vitro studies have proved that gemcitabine and irinotecan act synergistically [12,13]. Reportedly, combination chemotherapy with irinotecan and gemcitabine was more effective than

irinotecan monotherapy in patients treated for extensive small-cell lung cancer [23]. Synergic action may have contributed to the prolonged PFS in this study. iv) The severe toxicities of gemcitabine and irinotecan do not overlap in their adverse effect profiles. Diarrhea constitutes a dose-limiting toxicity of irinotecan, and the severity of diarrhea is significantly correlated with blood levels of 7-Ethyl-10-hydroxycamptothecin, the active metabolite of irinotecan [20]. Therefore, in this study, we set the initial dose of irinotecan to half the recommended dose. In contrast, dose intensity effects of gemcitabine are not reported, and the median PFS was only 3.6 months in studies that reported the administration of gemcitabine up to 1250 mg/m^2 on a weekly basis [24]. High dose intensity used as salvage chemotherapy does not always result in a survival benefit [19].

Reportedly, DCR and PFS rate at 6 months are useful surrogate markers of survival post progression [17]. A greater survival benefit is expected in patients receiving salvage chemotherapy with disease stabilization [10,11]. In this study, we expected that tailored-dose chemotherapy would be suitable as salvage chemotherapy to achieve high DCR and PFS rate at 6-months. We observed that compared with 7 of 13 patients (54%) showing PFS <6 months, 11 of 12 patients (92%) with PFS >6 months were re-administered platinum-taxane chemotherapy (p=0.073). In our view, re-administration of the platinum-based regimen contributed to prolonged survival post progression, as well as better OS [25]. A previous study reported that prolongation of the PFI with the administration of non-platinum agents in patients with partially sensitive recurrent ovarian cancer did not contribute to the survival benefit [26]. In contrast to this study, the patients enrolled in our study had platinum-resistant/refractory ovarian cancer. Our results suggest that patients who receive a non-platinum regimen with disease stabilization over >6-months may develop platinum-sensitive disease during the subsequent chemotherapy cycle [27].

Following are the limitations of our study: i) The initial treatment dose in this study was low, and tailored-dose chemotherapy could be associated with a risk of undertreatment. Some patients might have developed progressive disease before the tailored dose was escalated to the appropriate level because the initial dose administered was half the recommended dose determined by MTD. However, as shown in **Fig. 1**, 17 of the 25 patients investigated had mild toxicities during the first chemotherapy cycle, necessitating escalation of the drug dose to level 1 during the second cycle, which eliminated the risk of undertreatment. The overall prognosis of patients in this study was favorable; therefore, it is reasonable to conclude that the MTD-determined dose might not have affected survival outcomes in patients who received salvage chemotherapy. ii) In this study, one patient developed a gemcitabine-induced generalized eruption and discontinued gemcitabine therapy. Skin rash, abdominal pain, and flu-like symptoms secondary to gemcitabine administration are often observed within 1–2 cycles. Tailored-dose escalation to the appropriate level could not be performed following the onset of these symptoms in this patient. However, the other 24 patients did not experience these symptoms. Flu-like symptoms have been reported as dose-limiting factors by a phase I study [28]; administration of a low initial dose may have prevented the development of these symptoms in the patients investigated in our study. iii) We did not evaluate patients' quality of life. However, the hematological and non-hematological toxicity rates in this study were lower than those reported in patients who received conventional single-agent chemotherapy.

In conclusion, tailored-dose chemotherapy with gemcitabine and irinotecan was associated with a DCR of 75%, and PFS >6 months was observed in 48% of patients with platinum-refractory/resistant ovarian or peritoneal cancers. In this study, despite the use of two-agent

chemotherapy, the administration of the tailored-dose regimen could be continued with only mild toxicities. Gemcitabine and irinotecan may be suitable for salvage chemotherapy because these agents do not show cross-resistance with paclitaxel and carboplatin. Although conventional recommended doses cannot be administered to patients who receive tailored-dose chemotherapy, 16 of 25 patients in our study received a tailored dose (level 1) during the last (5th) cycle in this study. Therefore, it was reasonable to consider a starting gemcitabine dose of 750 mg/m^2 and an irinotecan dose of 50 mg/m^2 as dose level 1 in this study. The Avastin Use in Platinum-Resistant Epithelial Ovarian. Cancer (AURELIA) trial [29] has proved the efficacy of bevacizumab added to the regimen administered for platinum-resistant ovarian cancers; however, the chemotherapeutic regimens administered in the AURELIA study included pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan. Our study highlights the efficacy of gemcitabine and irinotecan combination chemotherapy. Large-scale multicenter phase II trials are warranted to investigate tailored-dose chemotherapy using gemcitabine and irinotecan in patients with platinum-refractory/resistant ovarian cancer or primary peritoneal cancer.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1
PFS and PFI.

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Supplementary Fig. 2
PFS and OS based on dose levels. (A) PFS and (B) OS. No significant differences were observed in dosage levels corresponding to PFS (log-rank test, p=0.807, Wilcoxon test, p=0.952) and OS (log-rank test, p=0.898, Wilcoxon test, p=1.000). PFS in the low (level –1, 0) and high (level 1, 2) dose groups was 7.2 months (95% CI=1.41–1.7) and 5.1 months (95% CI=2.0–13.8), respectively. The OS in the low- and high-dose groups was 14.5 months (95% CI=5.6–38.2) and 18.6 months (95% CI=5.6–34.1), respectively.

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Supplementary Fig. 3
Effect of stabilization on OS.

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REFERENCES

1. Bolis G, Parazzini F, Scarfone G, Villa A, Amoroso M, Rabaiotti E, et al. Paclitaxel vs epidoxorubicin plus paclitaxel as second-line therapy for platinum-refractory and -resistant ovarian cancer. Gynecol Oncol 1999;72:60-4.
PUBMED | CROSSREF
2. Monk BJ, Herzog TJ, Kaye SB, Krasner CN, Vermorken JB, Muggia FM, et al. Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010;28:3107-14.
PUBMED | CROSSREF

3. Buda A, Floriani I, Rossi R, Colombo N, Torri V, Conte PF, et al. Randomised controlled trial comparing single agent paclitaxel vs epidoxorubicin plus paclitaxel in patients with advanced ovarian cancer in early progression after platinum-based chemotherapy: an Italian Collaborative Study from the Mario Negri Institute, Milan, G.O.N.O. (Gruppo Oncologico Nord Ovest) group and I.O.R. (Istituto Oncologico Romagnolo) group. Br J Cancer 2004;90:2112-7.
PUBMED | CROSSREF
4. Sehouli J, Stengel D, Oskay-Oezcelik G, Zeimet AG, Sommer H, Klare P, et al. Nonplatinum topotecan combinations versus topotecan alone for recurrent ovarian cancer: results of a phase III study of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. J Clin Oncol 2008;26:3176-82.
PUBMED | CROSSREF
5. Lortholary A, Largillier R, Weber B, Gladieff L, Alexandre J, Durando X, et al. Weekly paclitaxel as a single agent or in combination with carboplatin or weekly topotecan in patients with resistant ovarian cancer: the CARTAXHY randomized phase II trial from Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO). Ann Oncol 2012;23:346-52.
PUBMED | CROSSREF
6. Felici A, Verweij J, Sparreboom A. Dosing strategies for anticancer drugs: the good, the bad and body-surface area. Eur J Cancer 2002;38:1677-84.
PUBMED | CROSSREF
7. Takahashi Y, Mai M, Sawabu N, Nishioka K. A pilot study of individualized maximum repeatable dose (iMRD), a new dose finding system, of weekly gemcitabine for patients with metastatic pancreas cancer. Pancreas 2005;30:206-10.
PUBMED | CROSSREF
8. Komatsu Y, Takahashi Y, Kimura Y, Oda H, Tajima Y, Tamura S, et al. Randomized phase II trial of first-line treatment with tailored irinotecan and S-1 therapy versus S-1 monotherapy for advanced or recurrent gastric carcinoma (JFMC31-0301). Anticancer Drugs 2011;22:576-83.
PUBMED | CROSSREF
9. Muthusamy P, Chary KV, Nalini GK. Metronomic chemotherapy: seems prowess to battle against cancer in current scenario. J Clin Diagn Res 2016;10:FC09-13.
PUBMED | CROSSREF
10. Cesano A, Lane SR, Poulin R, Ross G, Fields SZ. Stabilization of disease as a useful predictor of survival following second-line chemotherapy in small cell lung cancer and ovarian cancer patients. Int J Oncol 1999;15:1233-8.
PUBMED | CROSSREF
11. Gronlund B, Høgdall C, Christensen IJ, Engelholm SA, Hansen HH. Is stabilization of disease a useful indicator for survival in second-line treatment of ovarian carcinoma pre-treated with paclitaxel-platinum? Gynecol Oncol 2004;94:409-15.
PUBMED | CROSSREF
12. Bahadori HR, Rocha Lima CM, Green MR, Safa AR. Synergistic effect of gemcitabine and irinotecan (CPT-11) on breast and small cell lung cancer cell lines. Anticancer Res 1999;19:5423-8.
PUBMED
13. Gálvez-Peralta M, Dai NT, Loegering DA, Flatten KS, Safgren SL, Wagner JM, et al. Overcoming S-phase checkpoint-mediated resistance: sequence-dependent synergy of gemcitabine and 7-ethyl-10-hydroxycamptothecin (SN-38) in human carcinoma cell lines. Mol Pharmacol 2008;74:724-35.
PUBMED | CROSSREF
14. Rocha Lima CM, Green MR, Rotche R, Miller WH Jr, Jeffrey GM, Cisar LA, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 2004;22:3776-83.
PUBMED | CROSSREF
15. Takatani H, Soda H, Nakamura Y, Kinoshita A, Fukuda M, Nagashima S, et al. Phase I study of irinotecan and gemcitabine in previously untreated patients with advanced non-small cell lung cancer. Jpn J Clin Oncol 2007;37:353-7.
PUBMED | CROSSREF
16. 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;80:1239-47.
PUBMED | CROSSREF
17. Rose PG, Tian C, Bookman MA. Assessment of tumor response as a surrogate endpoint of survival in recurrent/platinum-resistant ovarian carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2010;117:324-9.
PUBMED | CROSSREF

18. von Stedingk H, Xie H, Hatschek T, Foukakis T, Rydén A, Bergh J, et al. Validation of a novel procedure for quantification of the formation of phosphoramide mustard by individuals treated with cyclophosphamide. Cancer Chemother Pharmacol 2014;74:549-58.
PUBMED | CROSSREF
19. Nakayama M, Kobayashi H, Takahara T, Nishimura Y, Fukushima K, Yoshizawa K. A comparison of overall survival with 40 and 50mg/m^2 pegylated liposomal doxorubicin treatment in patients with recurrent epithelial ovarian cancer: propensity score-matched analysis of real-world data. Gynecol Oncol 2016;143:246-51.
PUBMED | CROSSREF
20. Swami U, Goel S, Mani S. Therapeutic targeting of CPT-11 induced diarrhea: a case for prophylaxis. Curr Drug Targets 2013;14:777-97.
PUBMED | CROSSREF
21. Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol 2007;25:2811-8.
PUBMED | CROSSREF
22. 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;100:412-6.
PUBMED | CROSSREF
23. Pallis AG, Agelidou A, Agelaki S, Varthalitis I, Pavlakou G, Gerogianni A, et al. A multicenter randomized phase II study of the irinotecan/gemcitabine doublet versus irinotecan monotherapy in previously treated patients with extensive stage small-cell lung cancer. Lung Cancer 2009;65:187-91.
PUBMED | CROSSREF
24. von Minckwitz G, Bauknecht T, Visseren-Grul CM, Neijt JP. Phase II study of gemcitabine in ovarian cancer. Ann Oncol 1999;10:853-5.
PUBMED | CROSSREF
25. Colombo N, Gore M. Treatment of recurrent ovarian cancer relapsing 6-12 months post platinum-based chemotherapy. Crit Rev Oncol Hematol 2007;64:129-38.
PUBMED | CROSSREF
26. Pignata S, Scambia G, Bologna A, Signoriello S, Vergote IB, Wagner U, et al. Randomized controlled trial testing the efficacy of platinum-free interval prolongation in advanced ovarian cancer: the MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG study. J Clin Oncol 2017;35:3347-53.
PUBMED | CROSSREF
27. Bookman MA. Extending the platinum-free interval in recurrent ovarian cancer: the role of topotecan in second-line chemotherapy. Oncologist 1999;4:87-94.
PUBMED | CROSSREF
28. Delord JP, Raymond E, Chaouche M, Ruffie P, Ducreux M, Faivre S, et al. A dose-finding study of gemcitabine and vinorelbine in advanced previously treated malignancies. Ann Oncol 2000;11:73-9.
PUBMED | CROSSREF
29. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302-8.
PUBMED | CROSSREF