was considered to be more likely to be efficacious the longer the TFI was. Relapsing cases with a TFI < 6 months after the first-line platinum-based chemotherapy were considered likely to be 'platinum-resistant'; on the other hand, those cases with a TFI ≥ 6 months were considered likely to still be 'platinum-sensitive' [4–6]. Regimens other than repeating the initial chemotherapy were recommended for the quickly relapsing cases; however, patients with a TFI ≥ 6 months had a better chance of responding well either to a rechallenge with the initial platinum-based first-line treatment (such as TC therapy) or to certain other drugs. In the 'platinum-sensitive' cases, a combination chemotherapy using liposomal doxorubicin and carboplatin was demonstrated to be more effective than TC therapy [7]. Gemcitabine plus carboplatin was also shown to be more effective for 'platinum-sensitive' cases than carboplatin alone [8].

Among the 'platinum-sensitive' cases, those with a TFI of 6–12 months still exhibited a relatively worse response to second-line chemotherapy using carboplatin after a standard first-line TC therapy than those with a TFI of ≥12 months and were considered to be 'partially sensitive' cases [6]. For those ovarian carcinoma patients with 6–12 months of TFI after the first-line TC therapy, a combination chemotherapy of liposomal doxorubicin and carboplatin was shown to provide a better prognosis [9].

These findings were based on the theory of 'platinum-sensitivity'. To our knowledge, there has been little similar discussion related to relapse and 'taxane-sensitivity'. In the present study, the effectiveness of a combination chemotherapy using taxane with irinotecan or carboplatin as a second-line therapy after initial TC therapy was investigated to provide evidence for predicting 'taxane-sensitivity' in relapsing tumors.

Materials and methods

Patients

During the 7-year study period of 2002–2009, we conducted a prospective phase I/II study of a combination chemotherapy using docetaxel and irinotecan for TC-refractory or TC-resistant ovarian carcinoma cases (GOGO-OV2) (to be described in detail elsewhere). In brief, docetaxel and irinotecan were administered on day 1 and day 8, every 3 weeks, for the patients whose TFI was shorter than 6 months from the first-line TC therapy (175 mg/m^2 for paclitaxel and AUC 5 for carboplatin, every 3 weeks). In a phase I component, the recommended dose was determined to be 30 mg/m^2 (day 1 and day 8) for docetaxel and 50 mg/m^2 (day 1 and day 8) for irinotecan. On the other hand, the patients whose TFI was equal to or longer than 6 months from the first-line TC therapy were again treated with the same regimen as the initial TC therapy.

In the present study, the cases with a TFI < 6 months that were treated with a combination chemotherapy using docetaxel and irinotecan in a phase II component and the patients with a TFI ≥ 6 months who were treated with TC therapy were retrospectively analyzed.

Methods

In order to evaluate the therapeutic effect of the second-line chemotherapy, we used the previously described standard criteria from the World Health Organization [10] and others [11–13]. The tumors were assessed with a CT scan and/or MRI at baseline and every three treatment courses thereafter. A complete response (CR) was defined as the disappearance of all known disease, determined by two observations no less than 4 weeks apart. Partial response (PR) was defined as a 50 % or more reduction in the summed products of the two largest perpendicular dimensions of bidimensionally measurable lesions, for at least 4 weeks. Stable disease (SD) was defined as a less than 50 % decrease, or a less than 25 % increase, in tumor size, with no new detectable lesions. Progressive disease (PD) was defined as a greater than 25 % increase in tumor size, or as the appearance of new lesions.

Progression-free survival (PFS) was measured from the date of the last administration of chemotherapy to the date of the radiologic or pathologic denoted relapse, or to the date of the last follow-up. Overall survival (OS) was defined as the period from the start of chemotherapy to the patient's death, or to the date of the last follow-up, as previously described. TFI was defined as the period between the last administration of first-line chemotherapy and the initiation of the second-line chemotherapy, as previously described [14].

Statistical analysis of effect of second-line chemotherapy

Associations between the TFI and the patients' characteristics, including age, histology and initial stage, were analyzed by Pearson's Chi-square test. Association between sensitivity to second-line chemotherapy and TFI was analyzed by Fisher's exact test. PFS and OS curves determined by TFI were constructed using the Kaplan–Meier method and were evaluated for statistical significance by the log-rank test. The Bonferroni correction was used to assess differences among the three groups, and a value of $p < 0.017$ was considered statistically significant.

Results

Clinical characteristics of the study cases

During the 7-year study period, 145 patients underwent a second-line chemotherapy against a refractory or resistant disease, after having first received an adjuvant or salvage first-line chemotherapy using a TC regimen. The clinicopathological characteristics of these patients are shown in Table 1. Sixty-two patients with a TFI < 6 months received a combination chemotherapy of docetaxel and irinotecan; 36 patients with TFI = 6–12 months and 47 patients with TFI > 12 months were treated with this TC regimen.

Outcome of the patients after second-line chemotherapy

Only nine (15 %) of 62 patients whose TFI was shorter than 6 months exhibited sensitivity to a second-line chemotherapy using docetaxel and irinotecan; however, 13 (36 %) of 36 patients whose TFI was 6–12 months and 30 (64 %) of 47 cases >12 months responded to second-line TC therapy (Table 2).

The longer the TFI was, the higher the response rate was. The response rate of the cases with TFI = 6–12 months was significantly longer than that of those with TFI < 6 months, and that of those with TFI > 12 months was longer than that of those with TFI = 6–12 months ($p = 0.014$ and $p = 0.012$, respectively). These associations were statistically significant (Fisher's exact test with Bonferroni's correction).

Table 1 Clinical characteristics of the cases

TFI	<6–12 months	6–12 months	>12 months	*p* Value
Number	62	36	47	–
Age (years)				0.39
<60	39	20	33	
≥60	3	16	14	
Histology				0.08
Serous	40	26	34	
Endometrioid	7	5	6	
Clear	8	1	5	
Mucinous	6	0	1	
Others	1	4	1	
Initial stage				0.42
I/II	12	5	12	
III/IV	50	31	35	

Clinical characteristics of the cases with a TFI < 6 months after first-line TC therapy that were treated with a combination chemotherapy using docetaxel and irinotecan, the patients with a TFI = 6–12 months and those with a TFI ≥ 12 months, who were treated with TC therapy again, are shown. Association between TFI and the patients' characteristics, including age, histology and initial stage, was analyzed by Pearson's Chi-square test

TFI treatment-free interval

PFS and OS after second-line chemotherapy, by TFI

Differences by TFI in effectiveness of second-line chemotherapy regimens were investigated. The median PFS was 5 months (2–17 months) for 62 patients with TFI < 6 months, 8 months (1–65 months) for 36 patients with TFI = 6–12 months and 13 months (3–83 months) for 47 patients with TFI > 12 months. The longer the TFI was, the longer the PFS rate was. These associations were statistically significant ($p = 0.012$ and $p = 0.0011$, respectively) (log-rank test with Bonferroni's correction) (Fig. 1).

The median OS was 15 months (3–50 months) for 62 patients with TFI < 6 months, was 24 months (3–65 months) for 36 patients with TFI = 6–12 months and was 37 months (8–83 months) for 47 patients with TFI > 12 months. The longer the TFI was, the longer the PFS rate was. These associations were statistically significant ($p = 0.012$ and $p = 0.0005$, respectively) (log-rank test with Bonferroni's correction) (Fig. 2).

Conclusions

Chemotherapy plays an extremely important role in the treatment for ovarian carcinoma. Platinum has long been a key drug for ovarian carcinoma, and now a combination chemotherapy of platinum and taxane, especially TC therapy, is the gold standard for first-line regimens. For relapsed diseases, a second-line chemotherapy is usually performed. The effectiveness of this second-line chemotherapy was known to be associated with the TFI from the platinum-based first-line chemotherapy. The early relapsing cases, those with a TFI less than 6 months, were considered likely to be 'platinum-resistant', those with a TFI of 6–12 months were considered as 'partially sensitive' to platinum, and those with TFI ≥ 12 months were considered to be 'platinum-sensitive' [4–6].

Because platinum has been effectively used in the first-line chemotherapy, 'platinum-sensitivity' has often been used as the most important predictive factor of efficacy of second-line chemotherapy. However, taxane drugs, including paclitaxel and docetaxel, were also shown to be effective for ovarian carcinoma [15–17], and a combination TC therapy is currently regarded as a standard therapy. Under the specific circumstance that a TC therapy is used as the first-line chemotherapy, sensitivity not only to platinum but also to taxane may be a predictive factor for efficacy of the second-line chemotherapy.

Table 2 Association between TFI and effectiveness of a second-line chemotherapy using taxane

Second-line chemotherapy	Docetaxel + irinotecan	Paclitaxel + carboplatin	
TFI	<6 months	6–12 months	>12 months
CR	1	6	4
PR	8	7	16
SD	15	10	8
PD	38	13	9
Response rate (%)	15	36	64

The response rate of the cases with a TFI = 6–12 months was significantly better than that of those with TFI < 6 months, and that of those with TFI > 12 months was better than that of those with a TFI = 6–12 months ($p = 0.014$ and $p = 0.012$, respectively). These associations were statistically significant (Fisher's exact test with Bonferroni's correction)

TFI treatment-free interval, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

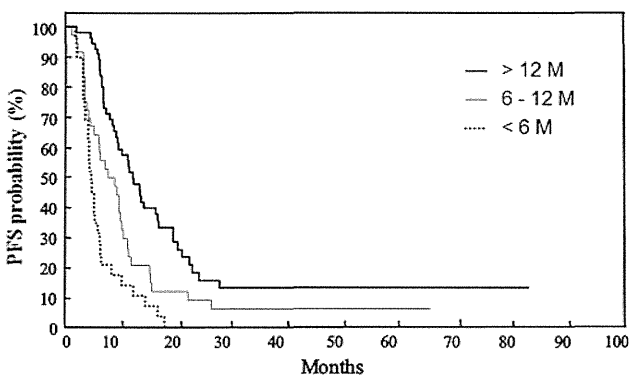

Fig. 1 PFS after second-line chemotherapy by TFI. The PFS of 62 patients with a TFI < 6 months was shorter than that of 36 patients with a TFI = 6–12 months, which was shorter than that of 47 patients with a TFI > 12 months. These associations were statistically significant ($p = 0.012$ and $p = 0.0011$, respectively) (log-rank test, with Bonferroni's correction) *PFS* progression-free survival

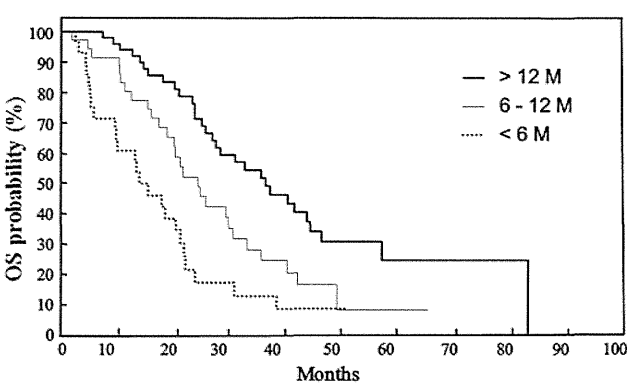

Fig. 2 OS after second-line chemotherapy by TFI. The OS of 62 patients with a TFI < 6 months was shorter than that of 36 patients with a TFI = 6–12 months, which was shorter than that of 47 patients with a TFI > 12 months. These associations were statistically significant ($p = 0.012$ and $p = 0.0005$, respectively) (log-rank test, with Bonferroni's correction) *OS* overall survival

Gronlund et al. [3] showed that retreatment with a TC regimen in the patients with TFI ≥ 6 months yielded a high response rate. There was a relative increase in response rates comparing TFI = 6–9 months ($n = 9$), TFI = 9–12 months ($n = 6$) and TFI > 12 months ($n = 22$), but the differences were not statistically significant, probably due to the small sample sizes.

Docetaxel exhibits a response rate of 22.4 % for those diseases which progressed either while undergoing therapy or within 6 months of completing therapy with paclitaxel and platinum [18]. Aravantinos et al. [19] reported that a response rate of 26.8 % was observed by treatment with docetaxel plus vinorelbine in 41 platinum-resistant and paclitaxel-pretreated patients who had a TFI < 6 months. Recently, Fu et al. [20] demonstrated that a PR was obtained by perifosine plus docetaxel in one (5 %) of 21 platinum- and- taxane-resistant or platinum-and-taxane-refractory high-grade ovarian carcinoma cases. Ushijima et al. [21] showed that a combination chemotherapy of docetaxel and irinotecan (the same regimen as in our study) exhibited a response rate of 6.3 % in the ovarian carcinoma cases with a TFI < 6 months (refractory or resistant) from a first-line chemotherapy, with at least two cycles of platinum and/or taxane. Polyzos et al. [22] also showed that six (20 %) of 30 paclitaxel-pretreated patients with likely platinum-resistant (TFI < 6 months) recurrences exhibited complete or partial response to a second-line docetaxel plus irinotecan regimen.

To our knowledge, the effectiveness of using a taxane-containing second-line chemotherapy in those patients previously treated with taxane-containing chemotherapy, especially the highly used gold standard TC therapy, has never been systematically investigated. In the present study, the effectiveness of a second-line combination chemotherapy using taxane with another drug (after a first-line TC therapy) was analyzed to redress that gap in our knowledge.

In the present study, 62 patients with a TFI < 6 months received a combination chemotherapy of docetaxel and irinotecan, and 36 patients with a TFI = 6–12 months and 47 patients with a TFI > 12 months were treated with a TC regimen. We were clearly able to demonstrate a significant association between the TFI after a first-line TC therapy and the response to a second-line chemotherapy containing taxane. The response rate of the cases with TFI = 6–12 months was significantly better than that of those with a TFI < 6 months, and the response rate of those with a TFI > 12 months was better yet than that of those with a TFI = 6–12 months ($p = 0.014$ and $p = 0.012$, respectively).

Moreover, a significant association between TFI after first-line TC therapy and the survival effect of the second-line chemotherapy using taxane with irinotecan, or carboplatin, was also demonstrated. The PFS of the cases with a TFI = 6–12 months was significantly longer than that of those with a TFI < 6 months, and that of those with a TFI > 12 months was longer than that of those with a TFI = 6–12 months ($p = 0.012$ and $p = 0.0011$, respectively). The OS of the cases with a TFI = 6–12 months was significantly longer than that of those with a TFI < 6 months, and that of those with a TFI > 12 months was longer than that of those with a TFI = 6–12 months ($p = 0.012$ and $p = 0.0005$, respectively).

These results imply that effectiveness of second-line taxane-containing chemotherapy is predictable by the TFI after first-line taxane-containing chemotherapy. Second-line regimens might thus be intelligently selected based on the likely 'taxane-sensitivity' of the relapsing tumor.

Paclitaxel and carboplatin therapy is currently used for ovarian carcinoma cases as a standard first-line chemotherapy all over the world. If the theory of 'taxane-sensitivity' can be applied for second-line chemotherapy in the same way as that of 'platinum-sensitivity', a combination chemotherapy of taxane with platinum, and other drugs, including liposomal doxorubicin and gemcitabine, might be effective. Markman et al. [23] showed a 25 % response of weekly paclitaxel even in TC-resistant cases. Weekly administration of taxane may be effective for some 'taxane-resistant' cases.

Our present study provides, for the first time, good evidence that the longer the TFI is after first-line taxane-containing chemotherapy, the more effective the second-line taxane-containing chemotherapy is likely to be, implying the model of 'taxane-sensitivity' may be applied for the second-line chemotherapy in the same way as that of 'platinum-sensitivity'. However, in our study, all the patients received platinum combined with taxane as the first-line chemotherapy, and those with late relapse (>6 months) were treated with a chemotherapy using platinum (carboplatin) combined with taxane. These data may reflect, in some part, platinum-sensitivity phenomenon. Further investigation is still required to establish an idea of 'taxane-sensitivity' and an efficacious strategy for second-line chemotherapy for advanced or recurrent ovarian cancer.

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Conflict of interest There are no conflicts of interest between the authors related to the research being reported.

Ethical standard This study was approved by our Institutional Review Board and Ethics Committee.

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ORIGINAL ARTICLE

Salvage chemotherapy for recurrent or persistent clear cell carcinoma of the ovary: a single-institution experience for a series of 20 patients

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Abstract
Background Recurrent or persistent clear cell carcinoma (CCC) of the ovary is particularly chemotherapy resistant. The purpose of this study was to review our extensive institutional experiences with recurrent or persistent CCC with the aim of finding a more effective chemotherapy regimen.
Methods The medical records of 67 patients treated for CCC of the ovary were retrospectively reviewed to select patients subsequently treated for recurrence or persistence of the disease.
Results The review identified 20 patients treated for recurrent or persistent CCC. For these 20 patients, 9 chemotherapeutic regimens, with 125 cycles, were administered. Gemcitabine monotherapy showed the best response rate [1 partial response (20%) and 2 stable diseases out of 5 patients so treated]. A partial response was observed with a combination of docetaxel plus irinotecan in 1 of 11 patients (9%). Stable disease was observed in 1 of 9 cases on a paclitaxel/carboplatin doublet and in 1 case on a docetaxel/carboplatin doublet. The median overall survival time was 8 months (range, 2–52). One group of patients who received gemcitabine therapy showed significantly better survival ($n = 5$, median 18 months) compared with a group who did not ($n = 15$, median 7 months) ($P = 0.0108$, by univariate analysis). In addition, multivariate Cox proportional hazards analysis revealed that gemcitabine administration was a significant factor for survival (hazard ratio: 13.0, 95% CI: 1.4727–115.2255, $P = 0.02$).
Conclusion Although most chemotherapeutic regimens for recurrent or persistent CCC have little or no effect, gemcitabine showed modest activity and is the most effective agent we have tested to date.

Keywords Chemotherapy · Clear cell carcinoma · Gemcitabine · Ovarian cancer · Persistence · Recurrence

Introduction

Epithelial ovarian cancer (EOC) is the second most lethal of the gynecological malignancies (after cervical cancer), causing approximately 125,000 deaths annually worldwide [1]. Standard therapy for EOC includes maximal surgical debulking followed by chemotherapy with platinum and taxane drugs. Despite an initial response rate to this primary therapy of approximately 80%, most EOC patients suffer subsequent recurrence and mortality.

Clear cell carcinoma (CCC) is a subtype of EOC that is relatively uncommon in western countries, including the USA, where CCC comprises only 5–10% of ovarian tumors. In contrast, in Japan, CCC has a higher incidence rate, at 20–25% of all EOCs. The reason behind this significantly higher incidence is not yet fully understood [2].

CCC has distinct biological activities relative to other histological types of ovarian cancer. Sugiyama et al. [3] have reviewed the distinct chemo-resistance and poorer prognosis of CCC. Enomoto et al. [4] showed that this problem continues, even with our best current standard regimen of a paclitaxel/carboplatin doublet.

For recurrent EOC, the treatment strategy depends on the tumor's response to the primary chemotherapy. When

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recurrence occurs more than 12 months after the completion of the initial therapy, re-administration of the same chemotherapy can be effective in many cases, resulting in extended survival times. However, if the recurrence occurs before 6 months have passed, most chemotherapeutic agents are usually no longer effective [5, 6].

Recurrences of the CCC subtype of EOC tend to be highly chemoresistant to any previous chemotherapy regimen, no matter when they reoccur. Some medical groups have attempted to overcome this resistance by a number of different strategies. Irinotecan (CPT-11) combined with cisplatin (CPT-P) was introduced as an efficacious regimen for refractory or recurrent general EOC, and has been used specifically for CCC. A retrospective Japanese multi-center study reported that a CPT-P group showed significantly better progression-free survival than a group receiving standard TP (taxane plus platinum) [7]. In another strategy, postoperative whole-abdominal radiotherapy (WAR) was carried out. The 5-year overall and disease-free survival in the WAR group was significantly better than that for the standard platinum-based chemotherapy group. However, the adverse effects in the bowel were occasionally severe, causing some patients to require surgery [8].

Clinical trials using novel agents specifically for CCC are ongoing. For persistent or recurrent disease, sunitinib is being evaluated in a phase II study by GOG (NCT 00979992, http://www.clinicaltrials.gov). Another phase II study is evaluating temsirolimus in combination with a paclitaxel/carboplatin doublet followed by temsirolimus consolidation as a first-line therapy in the treatment of stage III–IV CCC (NCT 01196429, http://www.clinicaltrials.gov). The results of these studies should give us a clue as to how to overcome CCC.

In this review, we recount our past experiences with recurrent and persistent CCC, seeking clues for overcoming the scourge that is CCC of the ovary.

Patients and methods

During the period of 1998–2009, 67 cases of CCC of the ovary (all of Japanese descent) underwent cytoreductive surgery within the Department of Obstetrics and Gynecology at the Osaka University Hospital, Osaka, Japan. The medical records of the patients were reviewed, revealing that the FIGO (International Federation of Gynecology and Obstetrics) staging of these cases was distributed as follows: stage I in 46 cases (Ia; 16 cases, Ib; 1 case, and Ic; 29 cases), stage II in 5 cases (IIc for all), stage III in 14 cases (IIIb; 3 cases, and IIIc; 11 cases), and stage IV in 2 cases.

Study inclusion eligibility criteria for those patients who were treated for recurrent or persistent disease included the following: (1) pathological diagnosis of CCC of the ovary at the initial surgery, (2) subsequent measurable recurrent or persistent disease, (3) treatment for the recurrent or persistent disease with one or more systemic chemoregimens, and (4) availability of adequate clinical information. The following patient information was abstracted from their medical records: age; date of primary surgery; residual disease; stage of disease based on FIGO criteria; date of completion of the primary chemotherapy; date of first detected recurrence or progression; regimens of each systemic agent administered; date of start and completion of each treatment; number of cycles of each systemic agent; response to each systemic agent administered; status at the last patient contact; and the date of last contact or death. Responses to the systemic agents were recorded according to version 1.0 of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Statistical analyses were performed using MedCalc for Windows (version 11.3.3.0, MedCalc Software, Mariakerke, Belgium). Treatment-free interval (TFI) was defined as the time (months) from the completion of initial therapy to recurrence with a radiological confirmation. For recurrent disease, overall survival time (OS) was calculated from the date of first recurrence to either the date of death or date of last contact. For persistent disease, OS was calculated from the date of primary surgery to either the date of death or date of last contact. A multivariate Cox proportional hazards analysis with selected variables was used to determine the significantly important factors for survivals. The Kaplan–Meier statistical method was used to calculate the overall survival times. Statistical significance was analyzed by the log-rank test. We considered the results to be significant when the P value was less than 0.05.

Results

After reviewing the medical records of 67 patients with CCC of the ovary, 21 patients were identified as having subsequently had a recurrence or a persistent disease. Of these 21 patients, 1 patient refused to receive any systemic agents and was therefore excluded from this study. A total of 20 patients received systemic agents, thereby meeting the eligibility requirements for this study, and were subsequently analyzed.

The characteristics of these 20 patients are shown in Table 1. The median age was 53 years; ages ranged from 35 to 65. In stage I patients, recurrence occurred in 4 cases with stage Ic (recurrence rate 9% for stage I overall, 14% specifically for stage Ic). There was also a single case of stage IIc, which thus showed a recurrence of 20%. Thirteen of 14 cases (93%) with stage III showed recurrence or persistent disease. Both cases with stage IV had persistent

disease (100%). Ten of the patients were known to still have residual disease after the initial debulking surgery (50%); the remaining 10 patients were classified as having had recurrent disease (50%). Retroperitoneal (pelvic and para-aortic) lymphadenectomy was performed in 12 cases in their initial surgeries (60%).

In our hospital, until 2003, postoperative chemotherapy with paclitaxel/carboplatin doublet (TC) was administered as the standard regimen for all EOC, regardless of histological subtype. Five of our 20-patient pool underwent this regimen. Thereafter, starting in 2003, because of the low response rate of this TC regimen, a docetaxel plus irinotecan (DIr) regimen was used for postoperative chemotherapy for advanced stages of CCC, and of these, 14 study patients received this regimen [4]. Among the 10 patients who had no detectable residual disease after initial surgery, but thereafter showed recurrence, 6 had equal to or more than 6 months of TFI, and the remaining 4 had less than 6 months of TFI.

Table 1 Characteristics of patients with recurrent or persistent clear cell carcinoma of the ovary

Characteristics	$n = 20$	%
Age		
Median	53	
Range	35–65	
FIGO stage		
I	4	20
II	1	5
III	13	65
IV	2	10
Residual disease		
No	10	50
Yes	10	50
Postoperative chemotherapy		
None	1	5
Paclitaxel/Carboplatin	5	25
Docetaxel/Irinotecan	14	70
Disease status		
Recurrence	10	
TFI: <6 months	4	20
TFI: ≥6 months	6	30
Persistent disease	10	50

FIGO International Federation of Gynecology and Obstetrics, *TFI* treatment-free interval

As shown in Table 2, 9 treatment regimens were administered. Paclitaxel/carboplatin doublet (TC) was administered to 9 patients, with a total of 28 cycles, where 1 cycle consisted of paclitaxel (175 mg/m^2) plus carboplatin (AUC = 5) every 3 weeks. A docetaxel/carboplatin doublet (DC) was administered for 1 patient, for a total of 3 cycles, where 1 cycle consisted of docetaxel (70 mg/m^2) plus carboplatin (AUC = 5) every 3 weeks. A weekly treatment of a paclitaxel/carboplatin doublet (wTC) was administered to 3 patients, for a total of 8 cycles, where 1 cycle consisted of paclitaxel (80 mg/m^2 on days 1, 8 and 15) plus carboplatin (AUC = 2 on days 1, 8, and 15) every 4 weeks. DIr was administered to 11 patients, for a total of 41 cycles, where 1 cycle consisted of docetaxel (30 mg/m^2 on days 1 and 8) plus irinotecan (60 mg/m^2 on days 1 and 8) every 3 weeks. The single-agent gemcitabine (GEM) was administered to 5 patients, for a total of 18 cycles, where 1 cycle consisted of gemcitabine (800 mg/m^2 on days 1, 8, and 15) every 4 weeks. The single-agent carboplatin was administered to 1 patient as a single cycle/single dose of AUC = 5. Oral etoposide was administered to 1 patient, for a total of 2 cycles, where 1 cycle consisted of oral etoposide (50 mg/day for 21 days) every 4 weeks. Pegylated liposomal doxorubicin (PLD) was administered to 1 patient for 2 cycles. One cycle consisted of PLD (40 mg/m^2 on day 1) once every 4 weeks. Wilms' tumor 1 vaccine (WT1) was administered to 2 patients, for a total of 22 cycles, where 1 cycle consisted of intradermal injections of an HLA-A*2402-restricted, modified 9-mer WT1

Table 2 Regimens and maximum responses for recurrent or persistent clear cell carcinoma of the ovary

Regimens	No. of patients	Total cycles	Median cycles	No. of maximum responses, duration
Docetaxel + Irinotecan	11	41	3	1 PR, 6 m
Paclitaxel + Carboplatin	9	28	3	1 SD, 7 m
Gemcitabine	5	18	4	1 PR, 6 m; 2 SD, 4 and 5 m
Paclitaxel + Carboplatin (weekly)	3	8	3	PD
WT1 vaccine	2	22	6	PD
Docetaxel + Carboplatin	1	3	3	1 SD, 4 m
Carboplatin	1	1	1	PD
Pegylated liposomal doxorubicin	1	2	2	PD
Oral etoposide	1	2	2	PD

PR partial response, *SD* stable disease, *PD* progressive disease

Table 3 Details of responders who showed more than stable disease with recurrent or persistent clear cell carcinoma of the ovary

Case	Age	Stage	Residual tumor (sites)	First-line regimen, cycles	TFI (when recurrent) or response (when persistent)	Second-line regimen, cycles	Response, duration	Third-line regimen, cycles	Response, duration	Fourth-line regimen, cycles	Response, duration	Fifth-line regimen, cycles	Response, duration	Status
1	65	Ic(2)	No	TC ×6	TFI; 31 m	DC ×3	SD, 4 m							DOD
2	42	IIIc	Yes (om, pnm, msty)	DIr ×6	PD	wTC ×3	PD	GEM ×3	PR, 6 m					DOD
3	54	IIIb	Yes (om, pnm)	DIr ×6	PD	TC ×3	PD	GEM ×10	SD, 5 m					DOD
4	51	IIc(2)	No	DIr ×6	TFI; 7 m	TC ×6	SD, 7 m	WT1 ×6	PD	GEM ×4	SD, 4 m	PLD ×2	PD	AWD
5	56	IIIc	No	DIr ×6, T ×12	TFI; 5 m	DIr ×6	PR, 6 m							AWD

Ic(2) and IIc(2) positive cytology of ascites, *om* omentum, *pnm* peritoneum, *msty* mesentery, *TFI* treatment-free interval (months), *DC* docetaxel + carboplatin, *TC* paclitaxel + carboplatin, *T* paclitaxel (consolidation), *wTC* weekly paclitaxel + carboplatin, *DIr* docetaxel + irinotecan, *GEM* gemcitabine, *WT1* Wilms' tumor 1 vaccine, *PLD* pegylated liposomal doxorubicin, *PR* partial response, *SD* stable disease, *PD* progressive disease, *DOD* dead of disease, *AWD* alive with disease

peptide every week [9]. Dose reduction was performed in response to toxicity to the patient's hematological status.

The majority of these administered regimens did not show significant responsiveness. A few showed some modest clinical activity. For example, gemcitabine represented the best response rate, in 1 of 5 patients (20%) it gave a partial response as a third-line treatment, and in 2 stable diseases it gave a response as a third- or fourth-line treatment. A partial response was also observed with DIr in one of 11 patients (9%) when used as a second-line treatment. Stable disease was observed in 1 of 9 cases treated with TC and in 1 case treated with DC, both as second-line efforts. Details of the responders who showed equal to, or more than, stable disease are shown in Table 3.

The median overall survival time of the recurrent or persistent patients was 8 months (range, 2–52), as shown in Fig. 1. Using univariate analysis, a group of patients who received gemcitabine therapy ($n = 5$) showed significantly better survival (median 18 months) compared with a group who did not receive it ($n = 15$, median 7 months) ($P = 0.0108$). A multivariate Cox proportional hazards analysis with selected variables (age, stage, postoperative chemotherapy, TFI, chemotherapy for recurrence or persistent disease) was used to determine the significantly important factors in survival. The analysis revealed that use of DIr for postoperative chemotherapy ($P = 0.02$) and use of gemcitabine for recurrence or persistent disease ($P = 0.02$) were significant factors in survival, as shown in Table 4.

Discussion

Clear cell carcinoma (CCC) of the ovary is relatively rare in the USA and Europe; however, its incidence in Japan

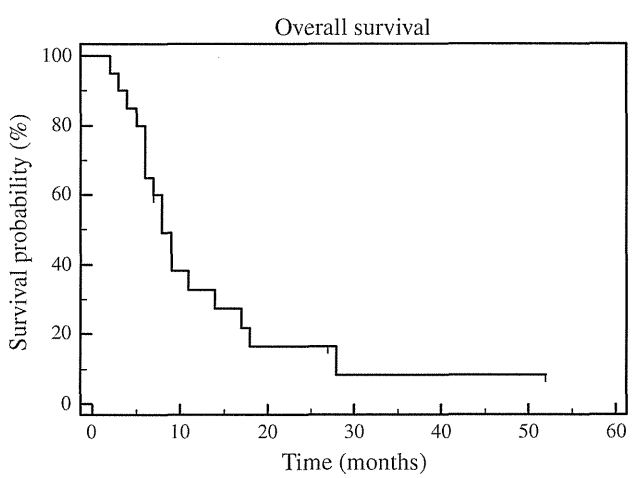

Fig. 1 Kaplan–Meier curve showing overall survival time of 20 patients with recurrent or persistent CCC. The median survival time was 8 months

Table 4 Multivariate Cox proportional hazards analysis for recurrent or persistent clear cell carcinoma of the ovary

Variables	Hazard ratio	95% CI	*P* value
Age			
<53 ($n = 9$)	1		0.18
≥53 ($n = 11$)	0.37	0.0898–1.6041	
Stage			
I/II ($n = 5$)	1		0.18
III/IV ($n = 15$)	6.16	0.4298–88.5383	
Postoperative chemotherapy			
TC ($n = 5$)	1		0.02
DIr ($n = 14$)	0.05	0.004–0.5792	
TFI			
<6 months ($n = 14$)	5.39	0.8834–32.9883	0.06
≥6 months ($n = 6$)	1		
Chemotherapy for recurrent or persistent disease			
DIr administration ($n = 11$)	1		0.23
Without ($n = 9$)	2.54	0.5407–11.9450	
TC administration ($n = 9$)	1		0.99
Without ($n = 11$)	0.99	0.2205–4.5342	
Gemcitabine administration ($n = 5$)	1		0.02
Without ($n = 15$)	13.0	1.4727–115.2255	

TFI treatment-free interval, *DIr* docetaxel/irinotecan, *TC* paclitaxel/carboplatin

accounts for roughly 20% of all EOC. We treated a total of 67 primary cases of CCC, along with 20 examples of recurrence or persistent CCC disease, during the 10-year study period from 1998 to 2009.

As previous reports have described, we also found that recurrent and persistent CCC was extremely chemoresistant. We noted that among the 9 different chemotherapy regimens we attempted, gemcitabine monotherapy showed the better response rate. Our patients who received gemcitabine therapy showed significantly better survival compared with a group who did not receive it. Furthermore, multivariate Cox proportional hazards analysis revealed that gemcitabine administration was a significant factor for survival (hazard ratio: 13.0, 95% CI: 1.4727–115.2255, $P = 0.02$). Therefore, we propose that gemcitabine may be an active chemotherapeutic agent for recurrent or persistent CCC.

Gemcitabine (2′,2′-difluorodeoxycytidine), a synthetic nucleoside analog of cytidine, has already been demonstrated to be an active agent for various other solid tumors, such as non-small-cell lung, pancreatic, genitourinary, and breast cancers [10]. As described in pioneering work from the Plunkett laboratory, gemcitabine is a prodrug that is metabolized to gemcitabine diphosphate and triphosphate, whose incorporation into DNA results in chain termination by inhibiting DNA polymerase activity [11]. Consequently, tumor cells are blocked in the G1 phase of the cell cycle. Gemcitabine triphosphate metabolite can be also incorporated into RNA, thus inhibiting RNA production [12].

Gemcitabine was studied for the first time as a single-agent treatment for recurrent EOC at a dose of 800 mg/m^2 on days 1, 8, and 15 every 28 days, thereafter, in a population of platinum-resistant ovarian cancers that included all histological subtypes [13]. In a review by Lorusso et al. [14], the results from a total of 411 patients treated by the single-agent gemcitabine were combined from 12 reports. The combined and re-analyzed data showed a mean gemcitabine response rate of 19%.

Recently, several large randomized control studies have been performed using gemcitabine in ovarian cancer patients. Mutch et al. have shown the safety and efficacy of gemcitabine monotherapy compared with PLD in their phase III trial in patients with platinum-resistant (Pt-R) recurrent ovarian cancer. In their report, gemcitabine and PLD seem to have comparable therapeutic indices, indicating that single-agent gemcitabine may be an acceptable alternative to PLD for patients with Pt-R recurrent disease [15]. For platinum-sensitive (Pt-S) recurrent disease, Pfisterer et al. reported that the addition of gemcitabine to carboplatin significantly improved progression-free survival and response rate compared with carboplatin alone without worsening quality of life in their phase III study [16]. Thus, gemcitabine is recognized as an active agent for both Pt-R and Pt-S recurrent ovarian cancer.

In most reports, gemcitabine's adverse effects and toxicity were easily manageable, transitory, noncumulative, and rarely represented a cause for dose reduction or treatment interruption. Gemcitabine has a well-proven activity in platinum and/or paclitaxel-resistant ovarian cancer patients, and seems to cause no cross-resistance with platinum compounds. However, it should be noted that

most of these studies represented treatments for mainly serous adenocarcinomas, with CCCs accounting for less than 5% of the cases. Therefore, the efficacy of gemcitabine for CCC is still largely unknown.

There are reports which suggest that gemcitabine may have a beneficial clinically active effect for CCC. Crotzer et al. [17] analyzed 51 patients treated for recurrent CCC. Their series received a total of 105 regimens with 344 cycles. In the platinum-sensitive setting, a partial response was observed in only 9% of cases, much lower than the response rates of 50–90% reported for platinum-sensitive disease in all cell types of EOC combined [18]. Among patients with platinum-resistant disease, only 1 patient had a partial response to gemcitabine and 1 patient had stable disease in response to 2 different regimens, paclitaxel and gemcitabine. Generally, second-line chemotherapy for platinum-resistant disease gives response rates of 15–20% when using an active agent.

Komiyama et al. [19] reported successful control with gemcitabine of a single case of peritonitis carcinomatosa presenting with massive ascites in a patient with a heavily pretreated recurrent CCC. Ferrandina et al. described a case of multi-drug-resistant CCC of the ovary showing a selective susceptibility to gemcitabine at first administration and again at re-challenge. Moreover, they showed that the tumor expressed a certain molecular profile that likely made it highly sensitive to gemcitabine [20]. Their finding points out that, although most reports of chemotherapy for CCC are highly disappointing, case-by-case molecular targeting therapy may be the key to combating this difficult to treat disease.

In conclusion, gemcitabine may be a key chemotherapeutic agent for the treatment of aggressive CCCs of the ovary. Additional adjunct molecular targeting therapy should also be considered.

Conflict of interest The authors declare that there are no potential conflicts of interest.

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Research Article

A phase II study of combination chemotherapy using docetaxel and irinotecan for TC-refractory or TC-resistant ovarian carcinomas (GOGO-OV2 study) and for primary clear or mucinous ovarian carcinomas (GOGO-OV3 Study)

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ABSTRACT

Objective: To analyze the efficacy and safety of combination chemotherapy of docetaxel and irinotecan for paclitaxel and carboplatin (TC) -refractory or -resistant ovarian carcinomas and for first treatment of primary clear cell and mucinous ovarian carcinomas.
Study design: Between 2002 and 2009, we conducted a prospective Phase II study of the efficacy and safety of combination chemotherapy using docetaxel and irinotecan in 62 patients with TC-refractory or -resistant ovarian carcinoma cases (GOGO-OV2) and 15 patients with primary clear cell and mucinous ovarian carcinoma cases (GOGO-OV3). The dose of docetaxel and irinotecan was determined during our previous Phase I study.
Results: A docetaxel plus irinotecan regimen provided a 53% response rate, 6 months progression-free survival (PFS), and 12 months overall survival (OS) for primary clear cell and mucinous ovarian carcinomas (similar to TC therapy). The differences of anti-tumor and survival effects between refractory and resistant cases were not statistically significant. The regimen also provided a 15% response rate, 5 months PFS, and 15 months OS for TC-refractory or TC-resistant cases, when used as a second-line chemotherapy. These data are similar to previous reports, however, our study provides the first data exclusively for the cases refractory or resistant to a gold standard TC therapy as a second-line chemotherapy. The regimen was demonstrated to be well tolerable.
Conclusion: Combination chemotherapy of docetaxel and irinotecan may be a useful option to treat TC-refractory/resistant cases and primary clear cell and mucinous adenocarcinoma cases of ovarian carcinoma.

1. Introduction

The major histological sub-types of ovarian carcinoma are serous, endometrioid, mucinous and clear cell adenocarcinomas. In the U.S., the serous adenocarcinoma sub-type represents 40–75% of all ovarian epithelial carcinomas, and clear cell adenocarcinomas equate to 5–10% [1–3]. We have recently discovered, however, that in Japan the clear cell adenocarcinoma sub-type accounts for a larger proportion of ovarian carcinoma cases (23%; our unpublished data).

Most ovarian carcinomas respond well to combination therapy of paclitaxel and carboplatin (TC therapy), but ovarian carcinomas of either the clear cell or mucinous histology sub-types have been recognized to often display a chemo-resistant phenotype, leading to a poorer prognosis. Conventional platinum-based

Abbreviations: CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RR, responsive rate; SD, stable disease; TC, paclitaxel and carboplatin; TFI, treatment-free interval; MDCT, multi-detector row computed tomography.

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chemotherapy regimens yield a poorer prognosis in patients with clear cell or mucinous ovarian carcinomas compared to patients with a serous sub-type [4]. A standardized effective treatment regimen for these platinum-resistant sub-types is needed. Irinotecan has been considered to be an effective treatment for mucinous adenocarcinoma of the ovary [5]. Irinotecan combined with cisplatin was also shown to be a promising regimen for clear cell cases [6].

Treatment of relapsed ovarian carcinoma is a more serious problem. Most patients first presenting with advanced disease will eventually relapse after treatment and die of a chemo-resistant disease [7–9]. Those relapsing cases with a treatment-free interval (TFI) of less than 6 months after their first-line platinum-based chemotherapy are considered likely to have a 'platinum-resistant' disease: on the other hand, those cases with a TFI $\geq$ 6 months are considered to have had a disease likely to still be 'platinum-sensitive' [10–12]. In 'platinum-sensitive' cases, combination chemotherapies using either liposomal doxorubicin plus carboplatin, or gemcitabine plus carboplatin, were demonstrated to be more effective than TC or carboplatin therapy alone [13,14].

For platinum-resistant relapsed cases, however, there has been no regimen established as a good standard therapy. There are promising options. Irinotecan has been shown to be a promising treatment for recurrent ovarian carcinomas [5]. Combination chemotherapy of docetaxel and oxaliplatin was also shown to be effective for recurrent ovarian carcinoma cases [15].

In the Phase II studies we demonstrate here, we demonstrate the efficacy and safety of combination chemotherapy of docetaxel and irinotecan for both TC-refractory (progression during TC therapy) or TC-resistant (TFI < 6 months after TC therapy) ovarian carcinoma cases (GOGO-OV2) and for treatment of primary clear cell and mucinous ovarian carcinoma cases (GOGO-OV3).

2. Materials and methods

2.1. Patients

During the 7-year study period of 2002–2009, we conducted a prospective Phase II study of a combination chemotherapy using docetaxel and irinotecan for TC-refractory or -resistant ovarian carcinoma cases (GOGO-OV2) and primary clear cell and mucinous ovarian carcinoma cases (GOGO-OV3). The dose of docetaxel and irinotecan was determined during our previous Phase I study. In brief, docetaxel and irinotecan were administered on day 1 and day 8, every 3 weeks. The recommended dose for TC-refractory or -resistant ovarian carcinoma cases (GOGO-OV2) was determined to be 30 mg/m^2 (day 1 and day 8) for docetaxel and 50 mg/m^2 (day 1 and day 8) for irinotecan. The recommended dose for primary clear cell and mucinous ovarian carcinoma cases (GOGO-OV3) was determined to be 35 mg/m^2 (day 1 and day 8) for docetaxel and 50 mg/m^2 (day 1 and day 8) for irinotecan.

2.2. Methods

In order to evaluate the therapeutic effect of chemotherapy, we used the previously described standard criteria from the World Health Organization (WHO) [16] and others [17–19]. Anti-tumor effect (complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD)) was evaluated with a multi-detector row computed tomography (MDCT) and/or MRI scan at baseline and every three treatment courses thereafter. Progression-free survival (PFS) was measured from the date of the last administration of chemotherapy to the date of radiologically or pathologically denoted relapse, or to the date of the last follow-up. Overall survival (OS) was defined as the period from the start of chemotherapy to the patient's death, or to the date of the last follow-up, as previously described.

Table 1
Clinical characteristics of the GOGO-OV2 cases. Clinical characteristics of the 62 patients who underwent combination chemotherapy of docetaxel and irinotecan against refractory or resistant ovarian carcinomas after TC therapy. TC refractory, cases whose diseases were demonstrated to be SD or PD during prior TC therapy; TC resistant, cases whose recurrences were diagnosed within 6 months after prior TC therapy.

Clinical characteristics	GOGO-OV2
Number	62
Age, median (years)	56 (39–73)
Histology	
Serous	40
Endometrioid	7
Clear cell	8
Mucinous	6
Others	1
Initial stage	
I/II	12
III/IV	50
Response to prior TC therapy	
Refractory	35
Resistant	27

3. Results

3.1. Clinical characteristics of the GOGO-OV2 cases and the GOGO-OV3 cases

During the 7-year study, 62 patients underwent combination chemotherapy of docetaxel and irinotecan against their refractory or resistant ovarian carcinomas (GOGO-OV2). The clinicopathological characteristics of these patients are shown in Table 1. All had received TC therapy as first-line chemotherapy, but were in failure or relapse. The median number of courses of combination chemotherapy of docetaxel and irinotecan was 3 (range 1–6).

We also studied 15 patients who received, as first-line treatment, combination chemotherapy of docetaxel and irinotecan against their primary clear cell or mucinous ovarian carcinomas (GOGO-OV3). The clinicopathological characteristics of these patients are shown in Table 2. All these patients first underwent primary cytoreductive surgery (mostly, hysterectomy, bilateral salpingo-oophorectomy and partial omentectomy, pelvic and para-aortic lymphadenectomy, and resection of metastatic lesions). Evaluable disease greater than 1 cm remained in each

Table 2
Clinical characteristics of the GOGO-OV3 cases. Clinical characteristics of the 15 patients who received first-line combination chemotherapy of docetaxel and irinotecan against their primary clear or mucinous ovarian carcinomas.

Clinical characteristics	GOGO-OV3
Number	15
Age, median (years)	60 (38–74)
Histology	
Clear cell	11
Mucinous	4
Status of the disease	
Primary	15
Stage	
I/II	0
III/IV	15
Recurrent	0

Table 3
Anti-tumor effect of a combination chemotherapy of docetaxel and irinotecan against TC therapy -refractory or -resistant ovarian carcinomas (GOGO-OV2). Refractory, the cases whose diseases were demonstrated to be SD or PD during their prior TC therapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Response rate, the rate of CR+PR; Disease control rate, the rate of CR+PR+SD.

	Refractory	Resistant	Total
CR	0	1	1
PR	4	4	8
SD	9	6	15
PD	22	16	38
Response rate	11%	19%	15%
Disease control rate	37%	41%	39%

case. The median number of courses of this combination chemotherapy was 6 (range 1–9).

3.2. Anti-tumor effect of docetaxel and irinotecan against TC-refractory or -resistant ovarian carcinomas (GOGO-OV2)

The combination chemotherapy of docetaxel and irinotecan was effective (PR) in 4 cases (11%) out of 35 resistant or recurrent ovarian carcinomas, which had been demonstrated to be refractory against TC therapy (Table 3). The refractory disease was stabilized in 13 of 35 cases (37%). Among the 27 resistant or recurrent ovarian carcinomas, which had demonstrated resistance against TC therapy, a CR was obtained in a single case, and PR was observed in 4 cases. The response rate was 19%. The diseases resistant against first-line TC therapy were stabilized in 11 cases (41%). The difference of anti-tumor effects between refractory and resistant cases was not statistically significant.

In total, combination chemotherapy of docetaxel and irinotecan was effective in 15%. The difference of the response rate and the disease control rate to the second-line chemotherapy was not significant between refractory and resistant cases.

3.3. Anti-tumor effect of combination chemotherapy of docetaxel and irinotecan against primary clear cell or mucinous ovarian carcinomas (GOGO-OV3)

Among the 15 primary clear or mucinous ovarian carcinomas with evaluable residual disease left after the cytoreductive surgery, CR was obtained in 2 cases, and PR was observed in 8 cases (Table 4). The response rate was 53%, and the disease control rate was 67%.

Table 4
Anti-tumor effect of combination chemotherapy of docetaxel and irinotecan against primary clear or mucinous ovarian carcinomas (GOGO-OV3). Anti-tumor effect of combination chemotherapy of docetaxel and irinotecan (GOGO-OV3) was compared to that of conventional TC therapy conducted in GOGO-OV1 (to be published elsewhere). Refractory, cases whose diseases were demonstrated to be SD or PD during prior TC therapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Response rate, the rate of CR+PR; Disease control rate, the rate of CR+PR+SD.

	Docetaxel irinotecan (GOGO-OV3)	TC (GOGO-OV1)
CR	2	0
PR	6	3
SD	2	4
PD	5	13
Response rate	53%[a]	15%
Disease control rate	67%	35%

The response rate of a combination chemotherapy of docetaxel and irinotecan was significantly higher than that of TC therapy.
[a] $p = 0.016$ (Fisher's exact test).

In a previous study we conducted, designated GOGO-OV1, TC therapy was demonstrated to be effective in 3 cases (15%) out of 20 primary clear cell or mucinous ovarian carcinomas (Table 4), which will be described elsewhere in the near future. The response rate to combination chemotherapy of docetaxel and irinotecan was significantly higher than that for conventional TC therapy ($p = 0.016$ by Fisher's exact test). The disease control rate also tended to be higher in the patients treated by docetaxel and irinotecan than those treated by TC therapy, but this tendency was not statistically significant, most probably due to the small sample size ($p = 0.064$).

3.4. PFS and OS after combination chemotherapy of docetaxel and irinotecan against resistant or recurrent ovarian carcinomas after TC therapy (GOGO-OV2)

The PFS and OS curves, constructed using the Kaplan–Meier method, of resistant or recurrent ovarian carcinomas after treatment with combination chemotherapy of docetaxel and irinotecan are shown in Fig. 1. The median PFS was 5 months (2–17 months) for the 62 refractory or resistant ovarian carcinoma patients. The median OS was 15 months (3–50 months). The differences of PFS and OS between refractory and resistant cases were not statistically significant.

3.5. PFS and OS after combination chemotherapy of docetaxel and irinotecan against primary clear or mucinous ovarian carcinomas (GOGO-OV3)

The PFS and OS curves of primary clear or mucinous ovarian carcinomas after treatment with first-line combination chemotherapy of docetaxel and irinotecan are shown in Fig. 2(a) and (b), respectively. The median PFS and OS of those treated by docetaxel and irinotecan were 6 (3–17) months, and 12 (5–42) months, respectively. Those after TC therapy in our GOGO-OV1 study are also shown in Fig. 2(a) and (b), for comparison of survival efficacy of combination chemotherapy of docetaxel and irinotecan and conventional TC therapy as first-line chemotherapy. The median PFS and OS of those treated by TC were 6 (2–43) months, and 13 (3–61) months.

Survival of the primary clear cell or mucinous ovarian carcinoma cases after combination chemotherapy of docetaxel and irinotecan was similar to that after conventional TC therapy

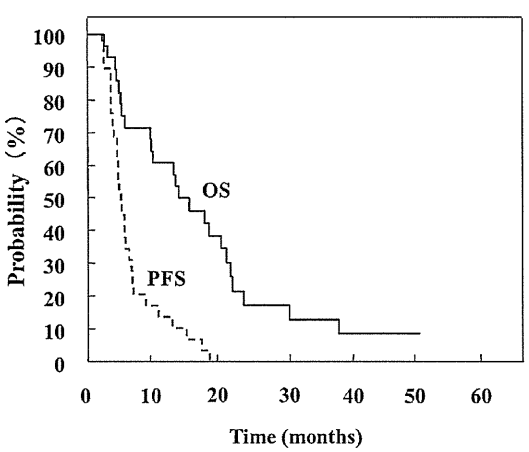

Fig. 1. PFS and OS after a combination chemotherapy of docetaxel and irinotecan against primary clear or mucinous ovarian carcinomas (GOGO-OV3). The median PFS and OS were 5 months (1–5 months) and 14 months (4–51 months), respectively. PFS: progression-free survival; OS: overall survival.

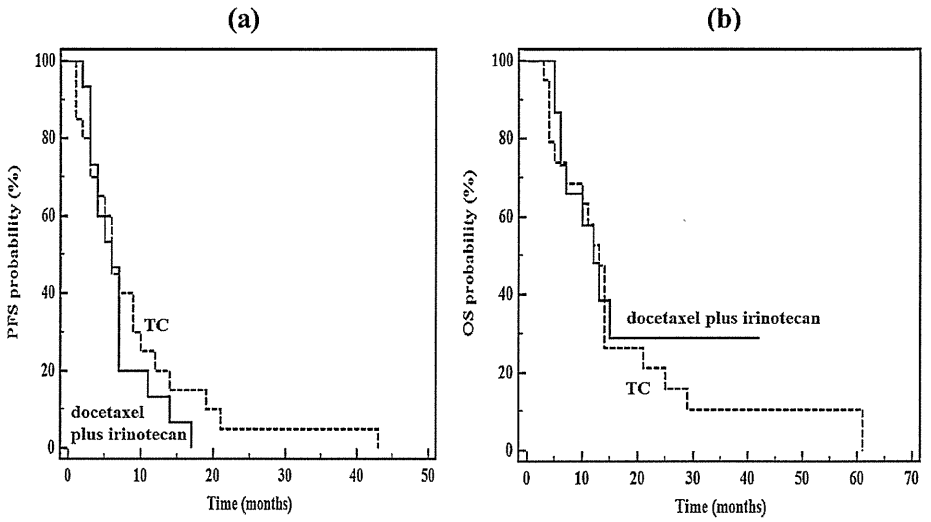

Fig. 2. PFS and OS after a first-line combination chemotherapy of docetaxel and irinotecan against primary clear cell or mucinous ovarian carcinomas (GOGO-OV3). (a) PFS after a combination chemotherapy of docetaxel and irinotecan (GOGO-OV3) compared to that after conventional TC therapy (GOGO-OV1) against primary clear cell or mucinous ovarian carcinomas The median PFS was 6 months (3–17 months) and 6 months (2–43 months) in GOGO-OV3 versus GOGO-OV1, respectively. PFS: progression-free survival. (b) OS after a combination chemotherapy of docetaxel and irinotecan (GOGO-OV3) compared to that after a conventional TC therapy (GOGO-OV1) against primary clear cell or mucinous ovarian carcinomas The median OS was 12 months (5–43 months) and 13 months (3–61 months) in GOGO-OV3 and GOGO-OV1, respectively. OS: overall survival.

($p = 0.42$ for PFS, and $p = 0.55$ for OS, by the log-rank test, respectively).

3.6. Adverse effects of combination chemotherapy of docetaxel and irinotecan (GOGO-OV2 and GOGO-OV3)

The major side-effects we observed of the combination chemotherapy of docetaxel and irinotecan are listed in Table 5. Grade 3 or 4 neutropenia was observed in 32% of cases in the GOGO-OV2 study group, and 20% in the GOGO-OV3 study. No peripheral neuropathy was detected in either the GOGO-OV2 and GOGO-OV3 studies.

In the GOGO-OV2 study, only 4 patients (6%) were unable to continue the recommended regimen for more than 3 courses. Two of these 4 patients acquired prolonged febrile Grade 4 neutropenia, one patient suffered from Grade 4 diarrhea, and the fourth patient refused to continue the chemotherapy due to Grade 3 nausea, except for those whose tumors demonstrated PD during 3 courses. However, a dose reduction was required in an additional 4 patients (6%).

In the GOGO-OV3 first-line treatment study, (with the exception for those whose tumors demonstrated PD during the 3 courses), only 1 patient (7%) could not continue the regimen for more than 3 courses; this was due to Grade 4 diarrhea; however, a dose reduction was required in another patient (7%).

Table 5
Adverse effects of combination chemotherapy of docetaxel and irinotecan (GOGO-OV2 and GOGO-OV3). Major side effects of combination chemotherapy of docetaxel and irinotecan are listed.

Grade 3 & 4	GOGO-OV2	GOGO-OV3
Leukopenia	17/62 (27%)	3/15 (20%)
Neutropenia	20/62 (32%)	3/15 (20%)
Anemia	7/62 (11%)	1/15 (7%)
Thrombocytopenia	5/62 (8%)	0/15 (0%)
Diarrhea	4/62 (6%)	1/15 (7%)
Nausea	5/62 (8%)	1/15 (7%)
Peripheral neuropathy	0/62 (0%)	0/15 (0%)

4. Comments

Platinum has long been a key drug for ovarian carcinoma, and now combination chemotherapy of platinum and taxane, especially TC therapy, is the gold standard for first-line regimens. Clear cell adenocarcinoma, however, has been shown to exhibit a higher resistance to platinum-based chemotherapy, leading to a poor prognosis for that sub-type [20]. In our previous GOGO-OV1 study, we found that clear cell carcinoma and mucinous adenocarcinoma were resistant to TC therapy [21] (to be described elsewhere). As yet there have been no reported regimens widely taking the place of conventional TC therapy for clear cell and mucinous adenocarcinomas.

In the present study (GOGO-OV3), the effectiveness and safety of first-line combination chemotherapy of docetaxel and irinotecan, for the evaluable clear cell or mucinous adenocarcinomas having residual tumor of >1 cm left after primary cytoreductive surgery, were analyzed. Among the 15 cases, including 11 clear cell carcinomas and 4 mucinous adenocarcinomas, 8 cases (53%) exhibited a complete or partial response (Table 4), indicating significant improvement ($p = 0.016$ by Fisher's exact test) over the results with conventional TC therapy found in our previous GOGO-OV1 study. The response was not significantly different between clear cell cases and mucinous cases (data not shown). Disease control was obtained in 12 cases (67%) in total. In spite of this promising response, PFS and OS were demonstrated to be similar to those following TC therapy (Fig. 2). These results suggest the strong anti-tumor effect of combination chemotherapy of docetaxel and irinotecan was transient. In another recent study, patients ($n = 99$) with clear cell carcinoma were randomly assigned to receive either TC therapy or combination chemotherapy of 60 mg/m^2 irinotecan on days 1, 8, 15, plus 60 mg/m^2 cisplatin on day 1, every 28 days. PFS tended to be longer in the latter group, although the difference was not statistically significant [6]. A regimen which provides a better prognosis than TC therapy has yet to be reported. The final results of the GCIG/JGOG3017 study, to compare TC and combination chemotherapy of irinotecan and cisplatin for clear cell carcinomas, are eagerly awaited.

Treatment of relapsed ovarian carcinomas, especially platinum-refractory or -resistant cases, is a severe problem. In our present GOGO-OV2 study, combination chemotherapy of docetaxel and irinotecan was tried, in 62 cases, as the exclusive second-line therapy for purely TC-refractory or -resistant ovarian carcinoma. A positive response was detected in 9 (15%) of the 62 cases, and disease control was obtained in 39% (Table 3). Refractory versus resistant cases did not exhibit any difference in response to the chemotherapy. The median PFS and OS were 5 months (2–17 months) and 15 months (3–50 months) respectively (Fig. 1). In a previous study, the efficacy of combination chemotherapy of docetaxel 60 mg/m^2 (day 1) and irinotecan 60 mg/m^2 (days 1 and 8) administered every 3–4 weeks, as second-line or third-line therapy, was evaluated in 32 platinum and/or taxane-refractory or -resistant cases [22]. The response rate was 6.3% and disease control rate was 34.4%. PFS and OS were 12.1 weeks and 45.3 weeks, respectively. These results were similar to those observed in our present study. A similar study was conducted for 31 patients, among whom 8 (26%) had primary tumors refractory to platinum compounds, and the rest of whom had received second-line treatments with either paclitaxel-ifosfamide-cisplatin or cisplatin-ifosfamide, and who had tumor recurrence within 6 months from the last exposure to platinum compounds [23]. Combination chemotherapy of docetaxel 60 mg/m^2 followed by irinotecan 200 mg/m^2 (both on day 1) with G-CSF support (days 2–6) every 3–4 weeks provided a 20% response (6 out of 30 cases), PFS of 5 months (2–17), and OS of 11 months (1–40), to those who had received first-line TC therapy. These results were similar to ours. Our study, however, provides the first data exclusively for the cases refractory or resistant to a gold standard TC therapy as second-line chemotherapy.

In the present study, adverse effects of combination chemotherapy of docetaxel and irinotecan were evaluated in both platinum-resistant cases (GOGO-OV2) and primary clear cell and mucinous adenocarcinoma cases (GOGO-OV3) (Table 5). Although grade 3 or 4 neutropenia was observed in 32% and 20%, of cases respectively, the results suggest that this recommended regimen is tolerable.

Our present study provides the first evidence that combination chemotherapy of docetaxel and irinotecan is as effective as TC therapy for primary clear cell carcinomas and mucinous adenocarcinomas. Our study also provides the first results for purely TC-resistant cases as second-line chemotherapy. Because TC therapy is one of the gold standard regimens for ovarian carcinomas, good clinical data for second-line chemotherapy after TC therapy failure are extremely important. Because the combination chemotherapy of docetaxel and irinotecan does not exhibit significant effectiveness, other large prospective studies to discover effective regimens are still required. Until then, combination chemotherapy of docetaxel and irinotecan may be used as an option to treat TC-refractory or -resistant cases and as a first-line treatment for primary clear cell or mucinous adenocarcinomas.

Statements of ethics

This study was approved by our Institutional Review Board and Ethics Committee.

Competing interest

There are no conflicts of interest between the authors related to the research being reported.

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ORIGINAL PAPER

WT1 peptide immunotherapy for gynecologic malignancies resistant to conventional therapies: a phase II trial

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Abstract
Objective The aim of the present study was to analyze the long-term survival effects of WT1 peptide vaccine, in addition to its anti-tumor effects and toxicity.
Methods A phase II clinical trial was conducted during the period of 2004–2010 at Osaka University Hospital, Osaka, Japan. The patients who had gynecologic malignancies progressing against previous treatments received WT1 peptide vaccine intradermally at 1-week intervals for 12 weeks. The vaccination was allowed to further continue, unless the patient's condition became significantly worse due to the disease progression.
Results Forty out of 42 patients, who met all the inclusion criteria, underwent WT1 peptide vaccine. Among these 40 patients, stable disease was observed in 16 cases (40 %). Skin toxicity of a grade 1, 2 and 3 occurred in 25 cases (63 %), 9 cases (23 %) and a single case (3 %), respectively, and liver toxicity of grade 1 in a single case (3 %). The overall survival period was significantly longer in cases positive for the WT1 peptide-specific delayed-type hypersensitivity (DTH) reaction after the vaccination, compared to those negative for the DTH reaction ($p = 0.023$). Multivariate Cox proportional hazards analysis demonstrated that the adjusted hazard ratio for the

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negative DTH reaction was 2.73 (95 % CI 1.04–7.19, $p = 0.043$).

Conclusion WT1 peptide vaccine may be a potential treatment, with limited toxicity, for gynecologic malignancies that have become resistant to conventional therapies. Larger scale of clinical studies is required to establish the efficacy of the WT1 peptide vaccine for gynecologic malignancies.

Keywords WT1 peptide immunotherapy · Gynecologic malignancy · Anti-tumor effect · Survival · Stable disease · Toxicity

Abbreviations

CR	Complete response
CT	Computed tomography
HLA	Human leukocyte antigen
HPV	Human papillomavirus
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PS	Performance status
RECIST	Response evaluation criteria in solid tumor
RR	Responsive rate
SD	Stable disease
TC	Paclitaxel and carboplatin

Introduction

The Wilms tumor gene, *WT1*, was first identified as a tumor suppressor gene responsible for Wilms tumors of the kidney. However, a series of investigations demonstrated that *WT1* possesses an oncogenic, rather than a tumor-suppressive, function, and WT1 protein is expressed in various kinds of hematological and solid malignancies, indicating that immunotherapy targeting WT1 could potentially be used for treatment of a variety of such malignancies (Oka and Sugiyama 2010). In fact, WT1 has been regarded as one of the most promising target antigens for cancer immunotherapy by an American National Cancer Institute pilot project (Cheever et al. 2009). It has already been demonstrated that WT1 vaccination is safe, and encouraging reports that showed its efficacy for several kinds of tumors have been accumulated (Oka and Sugiyama 2010; Hashii et al. 2010; Oji et al. 2010; Izumoto et al. 2008). A previous phase I study empirically determined a safe dose of the WT1 peptide, which was intradermally injected with Montanide ISA 51 adjuvant for patients with solid tumors, as 3 mg per injection, and this dose was shown to have little toxicity except skin reaction of the vaccination sites (Morita et al. 2006).

Ovarian carcinoma accounts for 5 % of all cancers among women and will eventually develop in 1 of every 58 women. It has an extremely high mortality rate; consequently, aggressive cytoreductive surgery followed by chemotherapy with taxane and platinum is the gold standard for its therapy. Endometrial carcinoma is an even more common malignant neoplasm of the female pelvis and is the fourth most common cancer of women today. Endometrial carcinoma is usually confined to the uterus or pelvis, has a lower mortality rate than ovarian cancer and is commonly treated by resection of the uterus and adnexae, with or without co-resection of the regional lymph nodes. Another common gynecological tumor, uterine cervical carcinoma, is mostly associated with a human papilloma virus (HPV) infection, and its incidence appears to vary from one locality to another. It is important to note that in some Asian and South American countries, cervical carcinoma accounts for the largest percentage of cancer deaths in women. Cervical carcinoma is usually treated by radical surgery and/or radiation therapy. And lastly, yet another kind of uterine tumor, the leiomyosarcoma, although rare, has an extremely poor prognosis (DiSaia and Creasman 2002).

Tumors in the early stage of all these diseases are usually treated relatively successfully, while the advanced and recurrent forms of these diseases are often very difficult to treat. Salvage, second-line and third-line chemotherapies are effective in only a fraction of the cases, and the best available supportive care is usually proposed to the patients whose tumors have become resistant to prior therapies.

An immunotherapeutic approach that is less toxic than available chemotherapies might be a more promising option for those whose gynecologic malignancies continue to progress despite conventional chemotherapy and radiation treatments. A previous small study showed that disease stabilization was achieved in 3 (25 %) of 12 gynecologic malignancies by vaccination with an antigenic WT peptide (Ohno et al. 2009). There is only one case report on the effect of WT1 peptide for the survival elongation in a ovarian cancer case (Dohi et al. 2011). In the present phase II trial, we have analyzed for the first time the long-term survival effect of the WT1 peptide vaccine, as well as its anti-tumor effects, evaluated by the usual response evaluation criteria in solid tumor (RECIST) and toxicity.

Materials and methods

Eligibility

This phase II trial was conducted at Osaka University Hospital, Osaka, Japan, during the period of 2004–2010. Major inclusion criteria were as follows: having a gynecologic malignancy progressing despite previous treatments;

WT1 protein expression in the primary or metastatic tumor tissue using anti-WT1 rabbit polyclonal antibody C-19 (Santa Cruz Biotechnology) or anti-WT1 mouse monoclonal antibody 6F-H2 (Dako Cytometry); positive status for human leukocyte antigen (HLA)-A*2402; performance status (PS) of 0–2; and life expectancy >3 months.

Vaccination schedule

The HLA-A*2402-restricted, 9-mer modified WT1 peptide (amino acids 235–243: CYTWNQMNL) emulsified with Montanide ISA 51 adjuvant, was used for the vaccination, as previously described (Hashii et al. 2010). The dose of WT1 peptide injected was 3 mg per body. The WT1 vaccination was scheduled to be performed intradermally every week for 12 weeks but was allowed to continue even after 12 weeks, unless the patient's condition became significantly worse due to the disease progression.

Evaluation of the WT1 vaccine effects

The primary endpoints of the WT1 vaccine study were its anti-tumor effect and its toxicity. Computed tomography (CT) was performed every 4 weeks to evaluate tumor size. The anti-tumor effect was evaluated by the RECIST (version 1.1) (Eisenhauer et al. 2009) after the vaccination during 12 weeks. Adverse effects were graded based on the National Cancer Institute's Common Toxicity Criteria (version 2.0). A test for delayed-type hypersensitivity (DTH) reaction specific to the WT1 peptide used for vaccination was performed at week 4 and 8. We regarded the patient as DTH positive, if the DTH reaction of the patient was positive either at week 4 or at week 8.

Secondary endpoints were progression-free survival (PFS) and overall survival (OS). PFS was defined as the period from the date of the start of WT1 vaccination to the date of the radiologic or pathologic relapse, or to the date of the last follow-up. OS was defined as the period from the start of the vaccination to the patient's death or to the date of the last follow-up. OS was analyzed for its association with DTH.

Cancellation or termination of WT1 vaccination

If grade 3 toxicity was observed, the next injection of the WT1 vaccine was postponed until the toxicity returned to grade 2 or less. The vaccination was permanently terminated if grade 4 toxicity was detected or if a performance status of 3 or worse was observed.

Statistical analysis

MedCalc (MedCalc Software, Mariakerke, Belgium) was used for statistical analysis. The association between DTH induction and anti-tumor effect, including RECIST evaluation, PFS and OS, was analyzed by Fisher's exact test. OS curves were constructed using the Kaplan–Meier method and evaluated for statistical significance by the log-rank test. Multivariate Cox proportional hazards model (stepwise method) for the factors including age, origin of the disease, histology, evaluation of the previous therapy and number of recurrence was calculated to evaluate whether DTH was a significantly important factor on OS. Results were considered to be significant when the p value was <0.05.

Statements of ethics

This study was approved by the Institutional Review Board and the Ethics Committee of the Osaka University Hospital. All patients provided written informed consent. (Approval of this analysis: #10302, approved on March 11, 2011).

Results

Clinical characteristics of the patients and completion rate of the study schedule

During the study period, 42 patients entered the study. Among these, 2 patients were excluded from the present analysis due to protocol violation. The clinicopathological characteristics of these patients are shown in Table 1. The median age was 56 (35–75). The histological diagnosis was obtained as ovarian carcinoma in 24 cases, cervical carcinoma in 11 cases, uterine sarcoma (leiomyosarcoma and carcinosarcoma) in 5 cases. These patients had already received 1–11 (median: 3) kinds of treatments prior to the WT1 vaccination and were considered to have disease

Table 1 Clinical characteristics of patients enrolled in the phase II study

Characteristics	
Number (cases)	40
Median age (years) (range)	56 (35–75)
Type of malignancy	
Ovarian carcinoma	24 (60 %)
Cervical carcinoma	11 (28 %)
Uterine leiomyosarcoma/carcinosarcoma	5 (13 %)
Performance status	
0	35 (88 %)
1	4 (10 %)
2	1 (3 %)
Median number of previous treatment regimens (range)	3 (1–11)

resistant to conventional therapies such as chemotherapy and radiotherapy.

Injection of the WT1 vaccine was performed weekly for 1–50 (median: 14.5) times. The 12 injections prescheduled upon entry to this trial were completed in 32 of the 40 cases (80 %). Vaccination was terminated prior to the 12th injection due to progression of the disease including worsening of PS in 8 cases (20 %).

Anti-tumor effect of the WT1 peptide vaccine evaluated by RECIST

Among the 40 patients who received the WT1 vaccination, neither complete response (CR) nor partial response (PR) was obtained. Encouragingly, however, stable disease (SD) of 3 months or more was observed in 16 cases (40 %), including 10 cases of ovarian carcinoma, 5 cases of cervical carcinoma and a single case of uterine leiomyosarcoma, respectively.

The WT1 peptide-specific DTH reaction appeared after the vaccination in 27 cases (68 %); however, the vaccine's anti-tumor effect evaluated by RECIST was not correlated to the appearance of DTH (data not shown).

Toxicity of the WT1 vaccination

An adverse effect was observed in 36 cases (90 %): grade 1, 2 and 3 of skin reaction in 25 cases (63 %), 9 cases (23 %) and a single case (3 %), respectively, and grade 1 liver toxicity in a single case (3 %). The skin reactions had definite relationship with WT1 injection because the reactions were observed only in WT1 injected area. The liver toxicity occurred after first injection of WT1, and the relationship between WT1 vaccine and liver toxicity was probable. Postponement of the next injection due to adverse effects occurred in one case with grade 3 of skin reaction. However, termination of the WT1 vaccine injection due to adverse effects was never required.

Prognosis of the patients treated with WT1 peptide vaccine: the vaccines' survival effect

The PFS was 84 days (11–497). Surprisingly, among these WT1-vaccinated cases, which had been already resistant to conventional therapies and the disease had exhibited continuous progression against various other treatments for 40–1,198 days (median: 185 days), progression-free survival for a range of 67–427 days (median: longer than 160 days) was achieved in 16 SD cases (Table 2). The median OS of all the patients was 193 days (29–941).

Although an association between an anti-tumor effect evaluated RECIST and an appearance of DTH reaction was not observed, the PFS tended to be longer in DTH-positive cases than DTH-negative ones ($p = 0.23$ by the log-rank test), and the OS was significantly longer in DTH-positive cases than DTH-negative ones ($p = 0.023$ by the log-rank test) (Fig. 1).

Table 2 Duration of disease progression before WT1 vaccination was begun and progression-free period afterward in stable disease (SD) cases

Case number	Duration of disease progression before WT1 vaccine (days)	Progression-free survival after WT1 vaccine (days)
1	40	105[a]
2	55	67
3	61	427[a]
4	81	320
5	97	126
6	142	145
7	155	92
8	178	273
9	192	140[a]
10	324	84
11	405	175
12	434	196
13	439	84[a]
14	655	196
15	737	219
16	1,198	180[a]
Median	185	160[a]

The duration of disease progression before the WT1 vaccine, and the progression-free period after the start of WT1 vaccination in 16 SD cases, is demonstrated

[a] The cases in which the disease was stable after WT1 vaccination without progression

Multivariate Cox proportional hazards analysis

We utilized the multivariate Cox proportional hazards model in order to find evidence to further support our belief that the DTH reaction was significantly associated with the survival. The DTH reaction was demonstrated to be an independent factor for overall survival of the patients (Table 3). The adjusted hazard ratio (HR) for the DTH reaction (− vs. +) was 2.73 (95 % CI 1.04–7.19, $p = 0.043$).

Discussion

A National Cancer Institute pilot project recently suggested that WT1 was one of the most promising targets for cancer immunotherapy (Cheever et al. 2009), and it has been demonstrated that WT1 vaccination is safe and has therapeutic potential for at least several kinds of tumors (Oka and Sugiyama 2010; Hashii et al. 2010; Oji et al. 2010;