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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in Japan the clear cell adenocarcinoma sub-type accounts for a larger proportion of ovarian carcinoma cases (23%; our unpublished data).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