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A Feasibility Study of Weekly Docetaxel with Capecitabine in Ovarian Cancer: A Promising Combination of Two Active Drugs with a Potential for Synergism

T. Safra[a] R. Bernstein Molho[a] J. Menzcher[c] M. Inbar[a] D. Grisaru[b] T. Levy[c]

Divisions of [a]Medical Oncology and [b]Gynecologic Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, and [c]Division of Gynecologic Oncology, Wolfson Medical Center, Holon, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Key Words
Ovarian cancer · Docetaxel · Capecitabine

Abstract
Objectives: To evaluate the safety and efficacy of weekly docetaxel with capecitabine in patients with recurrent/persistent epithelial ovarian cancer (EOC). ***Patients and Methods:*** Women treated for recurrent/persistent EOC in our department (January 2004 through December 2005) were recruited into this feasibility study. They received 35 mg/m^2 docetaxel on days 1 and 8 and 1,000 mg/m^2 capecitabine twice daily on days 1–14 in a 21-day cycle. ***Results:*** Nine patients were enrolled. The median age was 64 years (37–80). Time to progression ranged from 1.67 to 11.27 months: 1 had complete response, 3 had partial responses, 4 had stable disease and 1 had disease progression. There was no grade 3 or 4 bone marrow toxicity. Nonhematological toxicity included partial hair loss (n = 4), fatigue (n = 7), hand and foot syndrome (n = 2), diarrhea (n = 5) and fluid retention syndrome (n = 1). ***Conclusion:*** There was good antitumor activity but frequent moderate-to-severe nonhematological toxicities when weekly docetaxel and capecitabine were used as second-line therapy for recurrent EOC. Further investigation of this combination is warranted.

Introduction

Despite the development of more effective chemotherapy and the refinement of surgical techniques, ovarian cancer remains the number one cause of death from gynecological cancer in the western world [1]. Patients with relapsed or progressive epithelial ovarian cancer (EOC) are treated with agents such as topotecan, taxanes (paclitaxel, docetaxel, etc.), etoposide, liposomal doxorubicin, gemcitabine, or vinorelbine, or they are rechallenged with platinum-based therapy, all of which yield response rates of 10–30% [2]. 5-Fluorouracil (5-FU) had an important role in the treatment of EOC prior to the appearance of the new drugs, with a response rate of 5–23% [3–7]. Capecitabine is an oral prodrug of 5-FU which is converted at the tumor site to its active form by thymidine phosphorylase, an enzyme found in higher concentrations in tumor compared to normal tissues [8], adding a targeting quality to the drug which becomes active mainly in the tumor bed. Docetaxel, a chemotherapy known to be active in EOC by itself, induces upregulation of thymidine phosphorylase within the first 10 days of administration [9, 10]. Thymidine phosphorylase has a prominent role in the therapeutic index of capecitabine, and upregulation of the enzyme by docetaxel could result in increased activity in the tumor with limited increase in

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Dan Grisaru, MD, PhD
Head, Gynecologic Oncology Service, Department of Obstetrics and Gynecology
Lis Maternity Hospital, Tel Aviv Sourasky Medical Center
6 Weizmann Street, Tel Aviv 64239 (Israel)
Tel. +972 3 962 5622, Fax +972 3 962 5670, E-Mail grisaro@post.tau.ac.il

systemic toxicity. Docetaxel, an active drug in ovarian cancer with reduced myelosuppression in a weekly low-dose administration, combined with daily capecitabine and potentiated by upregulation of thymidine phosphorylase by docetaxel, are expected to be feasible and more effective. Finding the appropriate dose and schedule to maximize the therapeutic index is very challenging.

Several small phase II studies of capecitabine in heavily pretreated EOC patients reported response rates of 5–29% and a median time to progression (TTP) of 3.7 months. The most common side effects were hand and foot syndrome, nausea and vomiting, diarrhea, and mild myelotoxicity [11–15]. Docetaxel in recurrent EOC showed response rates of 23–40% [16–18]. The conventional every-3-week administration resulted in grade 3/4 neutropenia in more than 90% of the patients, and fatigue was also a frequent side effect. In breast cancer patients, weekly administration of docetaxel markedly reduced the severity of myelosuppression and fatigue, with a dose of 35–40 mg/m^2 having been found to be feasible and active [19].

Docetaxel and capecitabine (every 3 weeks) comprised the first chemotherapeutic combination to show a significant survival advantage over single-agent therapy in metastatic breast cancer [20], although at the expense of excessive toxicity. Later on, phase II studies of patients with advanced non-small cell lung cancer evaluated weekly docetaxel 36 mg/m^2 on days 1 and 8 and capecitabine 1,000 mg/m^2 twice daily for 2 weeks [21, 22]. The median duration of response was 6.2 months with a median overall survival of 17.8 months. The main side effects were hand and foot syndrome, diarrhea, nausea and vomiting with mild myelotoxicity [21]. Challenged by the idea of weekly docetaxel modulating capecitabine to a synergistic effect, several small studies in breast, lung and other cancers [23–26] were conducted and the results showed antitumor activity and moderate toxicity. The optimal dose and schedule could not yet be established. This combination of weekly docetaxel and capecitabine has not been evaluated in ovarian cancer, a disease sensitive to both drugs.

Our hypothesis is that the two active drugs with the potentiation of capecitabine by docetaxel and reduced docetaxel toxicity in a weekly administration might be a very active and feasible combination when given in the right schedule and doses. Since docetaxel induces upregulation of thymidine phosphorylase within the first 10 days of administration [9, 10], the women were given docetaxel on days 1 and 8. Capecitabine was administered on days 1–14 in order to take advantage of the enzyme's upregulation. We conducted this feasibility study in patients with EOC who had been previously treated with paclitaxel and carboplatin, to assess the efficacy and safety of this regimen.

Materials and Methods

From January 2004 through December 2005, 9 patients with recurrent or persistent EOC after one line of paclitaxel and carboplatin chemotherapy were enrolled into the study. They all had measurable disease as defined by bidimensional measurements (physical examination or radiologic techniques) or CA 125 abnormalities. The institutional review board approved the protocol, and informed consent was obtained from all patients. Intravenous docetaxel was administered at a dose of 35 mg/m^2 on days 1 and 8 and oral capecitabine at a dose of 1,000 mg/m^2 twice daily on days 1–14 every 21 days. Response was assessed by physical examination and CA 125 levels after each cycle of chemotherapy, and a computerized tomographic scan was performed every 3 cycles. Complete response (CR) was defined as disappearance of all tumor as evidenced by normalization of the serum CA 125 level, if initially elevated, and disappearance of all measurable lesions for at least one cycle of therapy or 4 weeks. A partial response (PR) was defined as a 50% or greater decrease in the products of the diameters of all measured lesions or a 50% or greater decrease in the serum CA 125 level compared with the pretreatment value that persisted for at least one cycle of therapy or 4 weeks, with no increase in the size of any lesion and with no evidence of new lesions. Disease progression (DP) was defined as any increase of 25% or more in the sum of the products of the diameters of any measurable lesion or in the estimated size of any nonmeasurable lesion, the appearance of an unequivocal new lesion, or a 100% increase in the serum CA 125 values. All other conditions were defined as stable disease (SD). Therapy was discontinued due to DP, intolerable toxicity or patient refusal. Platinum-sensitive disease was defined as disease recurrence after 6 or more months from completion of primary paclitaxel and carboplatin chemotherapy. Platinum-resistant disease was defined as recurrence after less than 6 months. TTP was evaluated from the first day of treatment until the first evidence of DP.

Results

Nine patients were enrolled. Their characteristics are summarized in table 1. Their pretreatment Eastern Cooperative Oncology Group performance status ranged from 0 to 1, and their median age was 64 years (range 37–80). Eight patients were initially diagnosed with advanced stage (III or IV) disease. Only 1 patient was initially diagnosed with early disease, stage 1C. Seven patients had platinum-sensitive and 2 had platinum-resistant disease. A median of 5 cycles (range 1.33–12.2) was administered. One patient had CR, 3 patients had PR, 4

Table 1. Patients' characteristics and results

Patient	Age years	Stage at diagnosis	Histology	Platinum sensitivity	DFI months	ECOG PS	Cycles n	Resp	TTP months
1	50	IIIc	serous	sensitive	15	0	2.2	DP	1.67
2	76	IV	serous	resistant	0	0	6.5	SD	5.17
3	37	IIIc	serous	sensitive	11	1	12.2	PR	9.50
4	69	IIIc	serous	sensitive	7	0	4.7	SD	4.60
5	63	IIIc	serous	resistant	5	1	6	SD	5.00
6	72	Ic	endometrioid	sensitive	31	0	5.3	CR	11.27
7	80	IV	serous	sensitive	8	1	1.33	SD	6.07
8	58	IIIc	serous	sensitive	8	0	6.8	PR	7.70
9	55	IIIc	serous	sensitive	7	1	2.6	PR	2.93

DFI = Disease-free interval (time from completion of primary chemotherapy to recurrence); ECOG PS = Eastern Cooperative Oncology Group performance status; Resp = response.

Table 2. Toxicity

	Frequency of grade of severity [1]			
	1	2	3	4
Hematological				
Anemia	1	1		
Thrombocytopenia				
Neutropenia	2			
Nonhematological				
Alopecia	3			
Nausea and vomiting		2		
Hand and foot syndrome	2			
Fatigue	3	3		
Diarrhea	3		2	
Edema			1	

[1] NIH CTC Version 2.0.

patients achieved SD and 1 patient had DP while on treatment. TTP ranged from 1.67 to 11.27 months (more than 6 months in 6 of the 9 patients).

There was no grade 3 or 4 bone marrow toxicity. The various adverse events are presented in table 2. Treatment was discontinued in 3 patients after 2–4 treatment cycles. Two women suffered from grade 3 diarrhea and fatigue requiring repeat hospitalization, intravenous fluid administration, dose reduction and treatment discontinuation, and 1 patient developed severe fluid retention syndrome.

Discussion

Our feasibility study of weekly docetaxel and capecitabine showed good antitumor response with modest to severe nonhematological toxicity. Previous studies in breast [20] and non-small cell lung cancer [21–26] showed that combining capecitabine with docetaxel improves therapeutic response. Furthermore, this regimen was the only combination that showed a survival advantage over single-agent treatment in breast cancer patients [20], probably related to the synergistic antitumor effect of both drugs via the upregulation of thymidine phosphorylase by docetaxel [9, 10].

In light of these data together with the known baseline activity of 5-FU in ovarian cancer, we were intrigued to evaluate the activity of capecitabine and docetaxel in patients with EOC. Docetaxel as monotherapy was shown to be active in platinum-sensitve and refractory recurrent EOC [16–18]. Single-agent capecitabine on the other hand was found to have only modest activity in recurrent EOC. In refractory and in heavily pretreated patients response rates of 8–9% were achieved [14, 15]. In patients with platinum-sensitive EOC recurring 6–12 months after completion of primary chemotherapy, a Gynecologic Oncology Group study achieved only 8% response rate [27] with median TTP of 3.9 months. Another phase II study [11] on a mixed population of platinum-sensitive and platinum-resistant EOC patients showed 29% response rate though with a similar median progression-free survival of 3.7 months.

Our feasibility study on a small number of patients demonstrated that the combination of weekly docetaxel

and capecitabine is active in recurrent EOC, with CR and PR having been observed in 4 patients, and the achievement of SD in 4 additional patients. TTP was relatively long, i.e. more than 6 months in 6 of the 9 patients. These results can be explained by the fact that most of our patients (7/9) had platinum-sensitive disease, ranging from 7 to 31 months (table 1). However, in view of the low response rate achieved even in platinum-sensitive patients using single-agent capecitabine, we believe that our encouraging results can be related to the combined treatment and to the specific administration schedule.

Since a regimen of capecitabine and docetaxel given every 3 weeks in breast cancer patients had resulted in severe toxicity [20], we chose to reduce the dose of capecitabine from 2,500 to 2,000 mg/m^2/day and to administer docetaxel in a weekly low-dose manner [19, 28]. Unlike the once every 3 weeks schedule of docetaxel administration, which was associated with dose-limiting myelosuppression and fatigue [18, 29], the weekly schedule of 35 mg/m^2 in our study resulted in only mild hematological toxicity and moderate fatigue. The capecitabine dose of 1,000 mg/m^2 b.i.d. resulted in a low rate of hand and foot syndrome. Two of the 9 study patients, however, suffered from grade 3 diarrhea and required repeat hospitalization, intravenous fluid administration, dose reduction and treatment discontinuation, and 1 patient developed severe fluid retention syndrome. This relatively high rate of severe side effects led us to reconsider the doses of the two drugs. We are now planning a phase II study with a capecitabine dose of 650 mg/m^2 twice a day as was previously suggested by Nadella et al. [10] with the same dose and schedule of docetaxel in platinum-resistant EOC patients.

Four of our 9 patients exhibited a therapeutic response (1 CR and 3 PR), 3 other patients achieved SD and most had no DP for more than 6 months. These favorable responses, albeit with substantial toxicity, might indicate clinical synergism or capecitabine potentiation by docetaxel.

The standard of care in platinum-sensitive recurrent EOC is a doublet of platinum combined with paclitaxel, docetaxel, gemcitabine or Caelyx or single-agent topotecan. In platinum-resistant patients usually each of these drugs is used although with disappointing results. Our current modest experience encourages us to recommend continued interest in the use of the combination of docetaxel and capecitabine for recurrent EOC in a setting of a larger clinical trial.

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