Retrospective Evaluation Of Weekly Docetaxel In Recurrent Ovarian Cancer: A Single Center Experience

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Citation

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Abstract

Background: The efficacy of weekly taxanes in the treatment of recurrent ovarian cancer is not widely known. We sought to investigate retrospectively the feasibility and efficacy of weekly docetaxel in this setting.

Patients and Methods: In our database, we found a total of 8 patients with recurrent ovarian cancer (7 patients with platinum refractory disease, and 1 platinum sensitive patient who could not be re-challenged with platinum) that were treated with weekly administrations of Docetaxel, 36 mg/m2/week, 6 out of 8 weeks (1 cycle).

Results: A median of 8 weeks of docetaxel was administered. Partial response was seen in the only platinum sensitive patient, and disease stabilization was encountered in 3 platinum refractory patients. No grade 3 or 4 hematological or non-hematological toxicity was apparent. Median progression free survival was 74 days.

Conclusions: Weekly docetaxel in this patient cohort is a non toxic treatment, but with limited evidence of activity.

INTRODUCTION

Recurrent ovarian cancer has poor prognosis with a median survival of 14 months ([1]). However, chemotherapy with various agents in this setting have been shown to induce tumor regression with no proven superiority of any agent or combination over the others in terms of prolonging survival, except a marginal survival difference demonstrated by intravenous over oral topotecan in the randomized trial by Gore et al ([2]). Unfortunately, patients with platinum refractory disease appear to derive less benefit from salvage chemotherapy when compared to patients with platinum sensitive disease ([3]).

Taxanes are among the chemotherapeutics used in the treatment of both chemonaive and recurrent ovarian cancer ([4,5,6]). However, weekly administration of taxanes is a relatively new approach and has not been fully tested in recurrent ovarian cancer. Indeed, so far, there is only one small phase 2 study of weekly docetaxel administration in recurrent ovarian cancer which only showed a modest activity with a response rate of 6.9% at the absence of severe side effects ([7]). As, it has been known for some time that weekly administration of taxanes may indeed have less toxicity ([8,9]), with some activity, we decided to collect retrospectively our experience of weekly docetaxel in recurrent ovarian cancer, to see the activity and toxicity of this regimen in our patients treated at the Akdeniz University Hospital.

PATIENTS AND METHODS

PATIENTS

In our oncology database and among the recurrent ovarian cancer patients treated at the clinics of obstetrics and gynaecology, and medical oncology departments of Akdeniz University Medical Faculty, we searched for cases that were treated with weekly docetaxel. At least one type of chemotherapy regimen before recruitment into the study, in the setting of platinum refractory (progression free survival (PFS) < 6 months), or platinum sensitive disease was required. Eastern Cooperative Oncology Group performance

status (ECOG) and the status of previous pelvic radiotherapy and prior docetaxel exposure were noted.

METHODS

Tumor response as evaluated by Computerized Tomography scanning and according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria was noted ([10]). CA-125 evaluations were also recorded, but not included in the assessment of response because of the absence of complete CA-125 data for the majority of cases.

Treatment schedule used in the treatment of our cases of recurrent ovarian cancer was docetaxel 36 mg/m2/week, 6 weekly administrations followed by a 2 weeks' rest period. This schedule was previously described in metastatic breast cancer ([8]). Also, in a recent study, a recommended dose level of 40 mg/m2/week was put forward, which is very close to the dose level used in this study ([11]). For the hypersensitivity prophylaxis, methylprednisolone 40 mg. was given orally, 3 times over 2 days, every week of chemotherapy administration (the evening before the day of treatment, the following morning and evening). 5-HT3 antagonists were used for the prophylaxis of emesis.

Toxicity data was collected from patient records and graded according to the National Cancer Institute (NCI) criteria ([12]). For practical purposes, if a specific type of toxicity was not mentioned in patient file, severe toxicity for this type was regarded to be absent.

The compliance with the following prechemotherapy suitability criteria were checked for each case: neutrophils $\geq 1.5\ 10^9$ /l and platelets $\geq 100\ 10^9$ /l before any infusion, with adequate renal and hepatic functions described as; total bilirubin less than or equal to the institutional upper limit of normal (ULN), alkaline phosphatase less than or equal to 2.5 x ULN, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than or equal to 1.5 x ULN, creatinine less than or equal to 1.5 mg/dl.

STATISTICAL ANALYSIS

PFS was assessed by Kaplan-Meier survival curves ([13]). At the time of analysis, all patients had been followed until progression, thus, the survival data was mature with no censoring used in the analysis.

RESULTS

PATIENT, DISEASE AND TREATMENT CHARACTERISTICS

A total of 8 cases were identified in our oncology database. Seven of 8 cases had platinum refractory disease, where as one patient (case no:4) had platinum sensitive disease, for whom the attending physician had felt that a re-challenge of platinum containing chemotherapy could have been more toxic than expected, since that patient had already received 9 cycles of Paclitaxel and Carboplatinum. The median age was 53 years (min:37 years, max:65 years). 4 patients had stage 3, and 4 had stage 4 disease with an ECOG performance status of 0 in 4, 1 in 2, 2 in 1, and 3 in 1 cases. There was no history of pelvic radiotherapy or previous docetaxel exposure. All patients had suitable organ functions before chemotherapy. Patient and disease characteristics are summarized in Table 1.

A total of 91 weekly administrations of Docetaxel were made. For each subject, a median of 8 weeks of Docetaxel was administered (min:3 weeks, i.e.less than 1 sequence, max:24 weeks, i.e.4 sequences).

TREATMENT EFFICACY

Best objective response was partial response in one and the only platinum sensitive patient. In the remaining 7 cases, disease stabilization was noted in 3 cases, early disease progression soon after the commencement of docetaxel was seen in 4 cases. Median PFS was 74 days (min:24 days, max:265 days). Please refer to Table 1 and Figure 1 for the PFS data. In the platinum refractory group, one patient (case no:8) deteriorated quickly, and died one month after the onset of therapy due to disease progression. Other 6 patients of this group and 1 platinum sensitive patient had progressive disease eventually, and had their treatment changed.

Figure 1

Table 1: Patient and disease characteristics, treatment outcome and toxicity

Patient No	Age	Stage	ECOG*	Site of metastasis	Previous regimens	Time since last chemotherapy (months)
1	42	3	1	peritoneum	7xcisplatin-epirubin- 5-FU, 6xPC**	1
2	56	4	1	lymph nodes	6xPC	1
3	59	3	3	peritoneum, colon	6xPC, 1xTopotecan	2
4	37	3	0	peritoneum	9xPC	12
5	65	4	0	liver, peritoneum	6xPC, 3xTopotecan	1
6	39	3	0	peritoneum	6xPC	2
7	50	4	0	lymph nodes, peritoneum	6xPC	4
8	57	4	2	lung, liver, bone, peritoneum	6xPC, 4xTopotecan	1

Figure 2

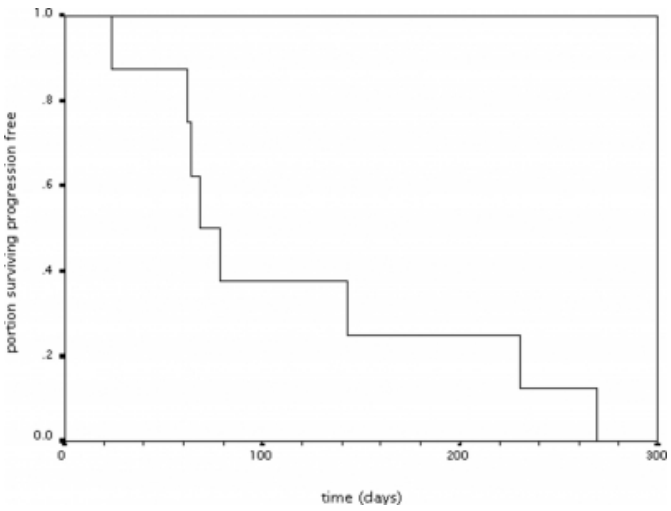
Patient No	Best objective response	PFS***(days)	Maximum toxicity
1	stable disease	64	Gr 1 neuropathy
2	stable disease	143	all grade 0 toxicity
3	progressive disease	68	all grade 0 toxicity
4	partial remission	269	all grade 0 toxicity
5	stable disease	230	Gr 2 thrombocytopenia
6	progressive disease	79	all grade 0 toxicity
7	progressive disease	62	all grade 0 toxicity
8	progressive disease	24	all grade 0 toxicity

Figure 3

*; Eastern Cooperative Oncology Group performance status
**; Paclitaxel and carboplatin
***; Progression free survival

Figure 4

Figure 1: Progression free survival on weekly docetaxel



TREATMENT TOXICITY

No grade 1 or higher hematological or non-hematological toxicity was noted in 6 patients. One patient developed grade 1 neuropathy at the 6th week of the 1st cycle, and another case had grade 2 thrombocytopenia at the 5th week of the 1st cycle, but none of them required dose modifications. No hypersensitivity reactions were seen. Complete grading of every individual non-hematological toxicity was absent in the medical records.

DISCUSSION

The results from this retrospective study show that weekly docetaxel administration is safe and feasible in recurrent ovarian cancer patients. Our findings support those from the paper by Berkenblit, et al. which again did not show any severe toxicity from this regimen in this heavily pretreated patient population ([7]). Again, in parallelism, it has been previously shown that weekly docetaxel administration could be associated with less hematological toxicity than the 3 weekly schedule, and also, neurotoxicity was increased with the weekly schedule ([11]). The lack of any grade 3 or 4 toxicity encountered during a total of 91 weekly administration of docetaxel in our study makes weekly docetaxel a non-toxic alternative in the treatment of recurrent ovarian cancer. However, caution is needed before clearly concluding that weekly docetaxel is a non-toxic regimen in this heavily pretreated patient cohort, since we could not administer multiple sequences of therapy to some of our cases, and this did not enable more reliable observation of toxicities.

Weekly docetaxel induced partial response in one platinum sensitive patient. To our knowledge, this is the first time demonstration of the efficacy of weekly docetaxel in platinum sensitive ovarian cancer. However, data from a single patient by no means implies the activity of this agent in platinum sensitive disease. Additionally, with this regimen, a patient with platinum resistant disease enjoyed progression free survival over 7 months. Although no tumor response was noted in platinum refractory patients in this study, achievement of long time progression free survival, as noted above, may imply that these patients can still get clinical benefit with weekly docetaxel. In accordance, weekly docetaxel had previously yielded disease stabilization for a duration of at least 2 cycles in 17% of cases in this setting ([7]), which is close to the figure of 22% (2/9 cases) from our cohort.

In the literature, tumor responses in the platinum refractory setting that are achieved by agents like oral etoposide, Gemcitabine, Tamoxifen and Topotecan are around 20%, although a very recent report of combination chemotherapy with Gemcitabine and cisplatinum demonstrates a much higher response rate ([14,15]). In this context, weekly docetaxel may also be an option, because of a previous case report of a platinum refractory ovarian cancer patient enjoying tumor regression with weekly docetaxel ([9]), apart from the results from a previously published phase 2 trial of weekly docetaxel ([7]), and the possibility of long time disease stabilization in a limited number of patients as seen in this study. It should not be forgotten that the possibility of long

time disease stabilization with weekly docetaxel is of clinical importance, since it was clearly shown that disease stabilization in recurrent ovarian carcinoma results in equal survival as achieved by partial responders to chemotherapy ([16]).

As a result, although this is a small retrospective analysis and may suffer from the related shortcomings, it is also the 2nd one to investigate the efficacy of weekly docetaxel in recurrent ovarian cancer, and also confirms that this regimen could yield modest clinical benefit in this patient cohort. So, given also the very low toxicity associated with this schedule, more phase 2 trials of weekly docetaxel in both platinum refractory and sensitive recurrent ovarian cancer patients, other than the trial from Berkenbilt, et al. ([7]), are warranted.

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