Cancer Chemother Pharmacol (2009) 64:297–300
DOI 10.1007/s00280-008-0870-z

ORIGINAL ARTICLE

# Biweekly docetaxel in recurrent ovarian cancer: a phase I dose finding study

**Johanna Mäenpää · Arto Leminen**

Received: 13 August 2008 / Accepted: 1 November 2008 / Published online: 20 November 2008


**Abstract**
*Purpose* To determine the maximum tolerated dose of biweekly docetaxel in patients with recurrent ovarian cancer, aiming at 70 mg/m$^2$.
*Methods* In this phase I trial, 8 patients were treated with biweekly docetaxel 50–65 mg/m$^2$. Dose-limiting toxicities were defined as any grade 3–4 non-hematological toxicity, prolonged ($\geq$1 week) grade 4 neutropenia or platelet count $<25 \times 10^9$/L, any neutropenic sepsis or febrile neutropenia, or any grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding.
*Results* Two groups of 3 patients each were given docetaxel 50 and 60 mg/m$^2$, respectively, and 2 patients received 65 mg/m$^2$. A total of 43 cycles were given; 26% of these were delayed, while granulocyte colony stimulating factor (G-CSF) support was used in 33%. The main toxicity was neutropenia: at dose levels of 50, 60, and 65 mg/m$^2$, grade 3–4 neutropenia occurred in 2/3, 3/3 and 1/2 patients, respectively. One patient experienced febrile neutropenia. A dose reduction was needed in 6 out of 13 cycles at the 65 mg/m$^2$ dose level. The study had to be closed prematurely due to the frequent need for G-CSF support, precluding the exploration of the 70 mg/m$^2$ dose. Non-hematological toxicities were mild. One patient had a partial response and six patients showed a stable disease.
*Conclusions* The maximum tolerated dose of biweekly docetaxel could not be determined in this study. It seems that increasing the dose beyond 60 mg/m$^2$ without a routine use of G-CSF is difficult.

**Keywords** Biweekly docetaxel · Recurrent epithelial ovarian cancer

J. Mäenpää (✉)
Division of Gynecologic Oncology,
Department of Obstetrics and Gynecology,
Tampere University Hospital,
P.O. Box 2000, 33521 Tampere, Finland
e-mail: johanna.maenpaa@pshp.fi

A. Leminen
Division of Gynecologic Oncology,
Department of Obstetrics and Gynecology,
Helsinki University Hospital, Helsinki, Finland

## Introduction

In the first line setting, the combination of docetaxel and carboplatin has similar efficacy as the gold standard in the treatment of ovarian cancer, or paclitaxel-carboplatin, with different safety pattern: the former is associated mainly with hematological toxicity, while neuropathy dominates the picture with the latter [1]. There exists no direct comparison between the taxanes in the second or the third line setting, but single-agent docetaxel in the dose range of 75–100 mg/m$^2$ seems to produce a response rate in the order of 30% [2].

Because 75–100 mg/m$^2$ of docetaxel every 3–4 weeks is associated with quite a pronounced neutropenia, with an up to 44% rate of febrile neutropenia in patients with recurrent ovarian cancer [2], attempts have been made to modify the dosing schedule. Patients with recurrent solid tumors seem to tolerate docetaxel 30–50 mg/m$^2$ biweekly quite well with response rates of 20 –50% [3–5]. Biweekly dosing of docetaxel could be an alternative also in case of ovarian cancer. The authors only know of one small phase I trial on biweekly docetaxel in ovarian cancer. However, the purpose of the study was to determine whether up to 60 mg/m$^2$ of biweekly docetaxel was feasible, rather than to clarify the maximum tolerated dose (MTD) [6].

The present study was undertaken to find out the MTD of biweekly docetaxel in recurrent ovarian cancer aiming at 70 mg/m$^2$, corresponding 105 mg/m$^2$ every 3 weeks.

## Patients and methods

The main inclusion criteria were as following: recurrent epithelial ovarian cancer, at least one measurable lesion by CT/MRI/US or an elevated (>60 kU/L) serum CA-125 level, age ≥18 years, reasonably fit to tolerate myelotoxic chemotherapy (ECOG 1-2, ANC ≥ 1.5 × 109/L, platelets ≥100 × 109/L, serum AST/ALT ≤1.5 × UNL, serum ALP ≤3 × UNL, serum bilirubin within normal limits, serum creatinine ≤1.25 × UNL). Both platinum-resistant and platinum-sensitive patients were included. The primarily platinum-sensitive patients were included only after the second relapse. However, after the second relapse, both secondarily platinum sensitive and resistant patients could be included.

The main exclusion criteria included pre-existing fluid retention, tumors of borderline malignancy, and peripheral neuropathy ≥grade 2.

A total of eight patients participated in the study (Table 1). The median age of the patients was 61.5 years. All patients had received a taxane–platinum combination as the first-line therapy for their ovarian cancer. The second line chemotherapy of the patients with primarily platinum sensitive disease had been either a taxane–platinum combination or the combination of gemcitabine and carboplatin.

Adverse effects were graded using the NCI Common Toxicity Criteria (NCI CTC version 2.0 modified).

A conventional dose escalation design for phase I trials of cytotoxic chemotherapy was used. The dose levels of biweekly docetaxel were 50, 60, 65, and 70 mg/m$^2$, respectively. Premedication included two 7.5 mg doses of oral dexamethasone given in the evening before the docetaxel 1-h IV infusion and approximately 1 h prior to the infusion. A third 7.5 mg dose of dexamethasone was administered 12 h after the infusion. Otherwise, conventional antiemetic treatment was used. A prophylactic granulocyte colony stimulating factor (G-CSF) use was not allowed. In case of a prolonged toxicity, the subsequent course could be postponed at most for 7 days.

The planned number of patients recruited at each dose level was 3–6. Following rules for dose escalation were complied with: if one out of three patients at a given dose level would experience a dose limiting toxicity (DLT) after at least one docetaxel infusion, two more patients were to be entered at the same dose level. If neither of these new patients would experience DLT, the dose was to be escalated to the next level. If at least 2 out of 3 or 3 out of 5–6 patients would experience the same DLT, this level would be considered as the MTD of biweekly docetaxel. After achieving the MTD, three confirmatory patients were to be recruited to the dose level immediately below the MTD in order to define the recommended dose of biweekly docetaxel.

The DLT was defined as any grade 3–4 non-hematological toxicity (except for alopecia), prolonged (≥1 week) grade 4 neutropenia or platelet count <25 × 10$^9$/L, any neutropenic sepsis or febrile neutropenia, or any grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding.

A written informed consent was obtained from all patients recruited to the study. Moreover, the study protocol was approved by the Ethics Committees of both participating hospitals.

## Results

A total of 43 chemotherapy cycles were administered during the study. Neutropenia was the main toxicity (Table 2). At dose levels 50, 60 and 65 mg/m$^2$, grade 3–4 neutropenia occurred in 2/3, 3/3 and 1/2 patients, respectively. However, only one occurrence of febrile neutropenia was encountered at the 60 mg/m$^2$ dose level. The same patient

**Table 1** The study population

| Patients | Age (years) | Histology and FIGO stage | Number of prior regimens | Dose (mg/m$^2$) | Measurable disease | Evaluable disease (Ca-125) |
|---|---|---|---|---|---|---|
| 1 | 64 | Undifferentiated St IIIC G3 | 1 | 50 | Yes | Yes |
| 2 | 54 | Serous St IIIC G3 | 1 | 50 | No | Yes |
| 3 | 58 | Serous St IIIC G3 | 2 | 50 | No | Yes |
| 4 | 62 | Serous St IV G3 | 1 | 60 | No | Yes |
| 5 | 54 | Endometrioid St IB G3 | 2 | 60 | No | Yes |
| 6 | 61 | Serous St IIIC G2 | 2 | 60 | Yes | Yes |
| 7 | 75 | Serous St IV G3 | 1 | 65 | Yes | Yes |
| 8 | 63 | Serous St IIIC G3 | 2 | 65 | No | Yes |

**Table 2** Grade 3–4 hematological toxicity by cycle, use of G-CSF, cycle delays, and dose reductions

| Dose | *n* | Grade 3 neutropenia | Grade 4 neutropenia | Febrile neutropenia | Use of G-CSF | Cycle delays | Dose reductions |
|---|---|---|---|---|---|---|---|
| 50 | 13 | 2 (15%) | 1 (8%) | 0 | 4 (31%) | 3 (23%) | 0 |
| 60 | 17 | 3 (18%) | 5 (29%) | 1 (6%) | 4 (24%) | 5 (29%) | 0 |
| 65 | 13 | 0 | 2 (15%) | 0 | 6 (46%) | 3 (23%) | 6 (46%) |
| All | 43 | 5 (12%) | 8 (19%) | 1 (2%) | 13 (33%) | 11 (26%) | 6 (14%) |

(#4) had another serious adverse event (SAE), or an infection, which was not associated with neutropenia, but led to hospitalization. These were the only SAEs reported during the study. There was no grade 3–4 anemia or thrombocytopenia reported, but patient #1 had Grade 2 anemia twice, while patient #4 had Grade 2 anemia once.

At all dose levels, one patient in each level needed at some point G-CSF support. In order to prevent any further febrile neutropenia, patient #4 was given G-CSF during the last four out of her five cycles. Four out of six cycles of patient #3 and six out of nine cycles of patient #8 were supported by G-CSF. Patients #1 and #6 experienced at some point cycle delays, too, but their treatment could be continued without any G-CSF support. In spite of the given G-CSF support, patient #8 needed a dose reduction (to 50 mg/m$^2$) in six of her treatment cycles. In fact, the actual total number of 65 mg/m$^2$ doses given during the study was only seven (patient #7, four doses; patient #8, three doses).

Non-hematological toxicity was mild and led in none of the cases to an interruption of the therapy (Table 3).

Using the Rustin criteria for a CA-125 response [7], only patient #5 showed a short-lived (2 months) partial response (Table 4). She had a non-measurable disease. Based on the CA-125 level and/or imaging findings, the disease was stabilized for 2 months (patients #4, #7 and #8), 3 months (patients #1 and #3), or 5 months (patient #6), respectively. The disease of patient #2 progressed from the very beginning of the therapy; therefore, she received only three doses of docetaxel.

**Table 3** The worst non-hematological side effects by patient

| Side effect | Grade 1 (*n*) | Grade 2 (*n*) |
|---|---|---|
| Fatigue | 4 | 4 |
| Nausea | 5 | 1 |
| Vomiting | 0 | 2 |
| Diarrhea | 1 | 0 |
| Pain | 4 | 1 |
| Stomatitis | 1 | 0 |
| Alopecia | 2 | 3 |
| Lacrimation | 0 | 2 |
| Edema | 3 | 0 |
| Weight loss | 0 | 1 |
| Sensory neuropathy | 1 | 0 |
| Motor neuropathy | 1 | 0 |

**Table 4** CA-125 responses

| Dose (mg/m$^2$) | Partial response | Stable disease | Progressive disease |
|---|---|---|---|
| 50 | 0 | 2 | 1 |
| 60 | 1 | 2 | 0 |
| 65 | 0 | 2 | 0 |
| All | 1 (12.5%) | 6 (75%) | 1 (12.5%) |

## Discussion

In this study, the idea was to try to escalate the dose of biweekly docetaxel up to 70 mg/m$^2$, or to the dose level, which would be more dose-intensive than 100 mg/m$^2$ given at the conventional Q3wk-dosing schedule. However, the MTD of biweekly docetaxel could not be determined. Febrile neutropenia experienced by patient #4 at the dose level of 60 mg/m$^2$ was the only DLT encountered during the study. Additionally, patients #3 (50 mg/m$^2$) and #8 (65 mg/m$^2$) were also given G-CSF, to prevent treatment delay beyond 7 days. Although this was in fact a protocol violation, it was undertaken for the sake of the patients' best interest. Because we thus had to use G-CSF support for three out of eight patients, and because, in spite of G-CSF support, patient #8 did not tolerate 65 mg/m$^2$, we made a decision to close the study prematurely. In the only other study of biweekly docetaxel in ovarian cancer known to the authors, Oishi et al. [6] alike had to use G-CSF support already at the dose level of 50 mg/m$^2$.

Our search for a dose-intensive regimen of biweekly docetaxel in recurrent ovarian cancer was stimulated by the encouraging results achieved with paclitaxel in this setting. In recurrent platinum and even paclitaxel-resistant ovarian cancer, paclitaxel at 80 mg/m$^2$ weekly is well tolerated and gives a response rate of up to 50% [8]. The high response rate is probably at least partly due to the fact that 80 mg/m$^2$ weekly is quite a dose-intensive regimen, corresponding to 240 mg/m$^2$ in the conventional 3-weekly dosing schedule. Although the results of both this study and the study by Oishi et al. [6] imply that such a dose-intensive regimen is not

feasible for biweekly docetaxel, a lower dose or 50–60 mg/m$^2$ of biweekly docetaxel seems to provide a reasonably well-tolerated alternative to patients with recurrent ovarian cancer.

In conclusion, biweekly dosing of docetaxel in recurrent ovarian cancer does not seem to allow for a more dose-intensive schedule than the conventional 3-weekly dosing.

**Acknowledgments** The study was partially supported by an educational grant from sanofi aventis Finland.

## References

1. Vasey PA, Jayson GC, Gordon A et al (2004) Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J Natl Cancer Inst 96:1682–1691
2. Kaye SB, Piccart M, Aapro M, Francis P, Kavanagh J (1997) Phase II trials of docetaxel (Taxotere) in advanced ovarian cancer—an updated overview. Eur J Cancer 33:2167–2170
3. Karavasilis V, Briasoulis E, Siarabi O, Pavlidis N (2003) Biweekly administration of low-dose docetaxel in hormone-resistant prostate cancer: pilot study of an effective subtoxic therapy. Clin Prostate Cancer 2:46–49
4. Vázquez S, Grande C, Amenedo A et al (2004) Biweekly docetaxel as second-line chemotherapy of patients with advanced non-small cell lung cancer: a phase II study of the Galician Lung Cancer Group (GGCP 006–00). Anticancer Drugs 15:489–494
5. Bamias A, Bozas G, Antoniou N et al (2008) Prognostic and predictive factors in patients with androgen-independent prostate cancer treated with docetaxel and estramustine: a single institution experience. Eur Urol 53:323–331
6. Oishi T, Kigawa J, Fujiwara K et al (2003) A feasibility study on biweekly administration of docetaxel for patients with recurrent ovarian cancer. Gynecol Oncol 90:421–424
7. Rustin GJ, Nelstorp AE, McLean P et al (1996) Defining response of ovarian cancer to initial chemotherapy according to S–Ca 125. J Clin Oncol 14:1545–1551
8. Kaern J, Baekelandt M, Tropé CG (2002) A phase II study of weekly paclitaxel in platinum and paclitaxel-resistant ovarian cancer patients. Eur J Gynaecol Oncol 23:383–389