*Anti-Cancer Drugs 1996*, **7**, pp. 398–401

# Preliminary report of the activity of docetaxel in advanced or recurrent squamous cell cancer of the cervix

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**Eighteen patients with squamous cell cancer of the cervix were treated with i.v. docetaxel 100 mg/m$^2$ over 1 h every 21 days. No patient received prior chemotherapy, except as a radiation sensitizer. Median age was 42 years (range 30–58) and Zubrod performance status was 1 (0–2). Ten (59%) patients had prior surgery and 11 (65%) had prior radiation therapy. Sixteen patients were evaluable for response. Two patients had a partial response (13%; 95% CI 0–32%) and eight (50%; 95% CI 23–77%) had stable disease. Dose reduction to 75 mg/m$^2$ was required in 10 patients and to 55 mg/m$^2$ in one patient. Granulocytopenia was the major hematopoietic toxicity (31% grade 3 and 44% grade 4). Docetaxel is active in patients with squamous cell cancer of the cervix and may be tolerable at this dose schedule.**

*Key words*: Cervix cancer, docetaxel, granulocyte colony stimulating factor.

## Introduction

Over the past four decades, the incidence and mortality rates for uterine cervical carcinoma have decreased in the US by as much as 70–75%.[1] However, cervical cancer remains a significant problem. It is the most common cancer of women in many parts of the world.[2] In the US, it is the seventh most common cancer in women. In 1995 it was estimated that 15 800 new cases were found and 4800 deaths were caused by cervical cancer.[3]

Surgery and radiation therapy are effective in treating most cases of early cervical carcinoma. Accordingly, chemotherapy has traditionally been used for the palliative management of advanced or recurrent disease that can no longer be managed by the other two modalities. Among the chemotherapeutic agents used for cervical cancer, the ones that have demonstrated the most consistent activity as single agents are cisplatin and ifosfamide with response rates of 21–31 and 33–50% in various dose schedules, respectively.[4–6] Irinotecan (CPT-11), a semisynthetic camptothecin analog, induced response rates of 24 and 27% in two recent reports.[7,8] Lower response rates are generally seen in patients who have had prior chemotherapy. Responses are also decreased in previously irradiated sites. The duration of response with single agents is brief, usually ranging from 4 to 6 months, with survival durations ranging from 6 to 9 months. The prognosis for advanced and recurrent disease remains poor, mainly because there is no effective systemic therapy.

Paclitaxel is a taxane alkaloid extracted from the Pacific yew (*Taxus brevifolia*).[9] It inhibits tubular disaggregation.[10,11] Several clinical studies have demonstrated paclitaxel's activity in advanced and refractory solid tumors.[12] Furthermore, response rates of 44–70% were seen after treatment with paclitaxel in squamous cell cancer of the head and neck[13,14] and esosphagus.[15]

Docetaxel is a taxane alkaloid similar to paclitaxel.[16] It is synthesized from a precursor molecule which is extracted from the needles of the European yew (*Taxus baccata*).[11] It also has a broad spectrum of activity in solid tumors.[12] In squamous cell cancer of the head and neck, docetaxel induces a 32% response rate.[17] These data support the assumption that docetaxel, like paclitaxel, may be active in squamous cell cancers. We report the preliminary results of a single center clinical study of docetaxel in patients with advanced or recurrent squamous cell cancer of the cervix.

This trial was supported by the National Cancer Institute.

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## Materials and methods

Women, 18 years of age or older, having measurable inoperable, recurrent or metastatic, histologically confirmed squamous cell carcinoma of the cervix were eligible. Patients were stratified according to whether or not they had positive serology for the human immunodeficiency virus (HIV). Patients must have had a Zubrod performance status of 0–2 and an expected survival of at least 3 months. Four weeks or more must have elapsed since any prior major surgery or radiation therapy (2 months if irradiation to more than 25% of the bone marrow). Chemotherapy, given as a radiation sensitizer only, must have been followed by a minimum of 1 year without evidence of disease. Furthermore, they were required to have an absolute granulocyte count of at least 1500 cells/$\mu$l, platelet count $\geq 100\,000/\mu$l, Hg $\geq 8.0$ g/dl, serum creatinine $\leq 1.5$ mg/dl, total bilirubin $< 1.0$ mg/ml, serum transaminase $\leq 2$ times the upper limit of normal if liver metastases were absent by abdominal CT scan or $\leq 4$ times the upper limit of normal if liver metastases were present. All patients signed an informed consent form. Patients were excluded if they were pregnant, lactating or of child-bearing potential (unless using effective contraception), had brain or leptomeningeal metastases or symptomatic peripheral neuropathy grade 2 or less or allergy to polysorbate 80.

Patients were entered consecutively into this phase II trial without randomization. All patients received docetaxel at an initial dosage of 100 mg/m$^2$ given as a 1 h i.v. infusion every 21 days. The dose of docetaxel could be escalated to 115 mg/m$^2$ or reduced to 75 mg/m$^2$ or even 55 mg/m$^2$. All patients were followed for objective and subjective evidence of toxicity. Patients had to receive a minimum of two complete cycles of docetaxel to be evaluable for response to therapy. However, patients who progressed after the first cycle were also considered evaluable for response. Patients who demonstrated a response to therapy continued to receive treatment with docetaxel for 6 months past the date of maximal response. Patients whose best response was stable disease could continue until disease progression. Patients were removed from study if they experienced unacceptable toxicity or progression. Premedication consisted of diphenhydramine hydrochloride 50 mg administered i.v. 30 min before the infusion of docetaxel. Patients who experienced hypersensitivity reactions to docetaxel were administered dexamethasone 20 mg i.v. or by mouth 12 and 6 h prior to docetaxel in addition to diphenhydramine 50 mg i.v. 30 min prior to docetaxel. Neupogen [granulocyte colony stimulating factor (G-CSF)] 5 $\mu$g/kg/day was administered s.c. as needed in neutropenic patients until recovery of the counts. If G-CSF was required then the dose of docetaxel was reduced for the next cycle. Moreover, prophylactic G-CSF was not permitted during the next cycle. The docetaxel dose was escalated if the granulocyte nadir count was greater than 1500 cells/$\mu$l and the platelet count was greater than 100 000/$\mu$l. The dose was reduced by one level for symptomatic neutropenia (less than 500 cells/$\mu$l) lasting less than 7 days or asymptomatic neutropenia lasting longer than 7 days. Non-hematologic toxicity allowed an increase by one level if there was grade 0–1 toxicity; however, grade 3–4 toxicity required a decrease of one level or stopping of the treatment. No dose schedule alterations were made for alopecia. All courses were held pending hematologic recovery to granulocytes $\geq 1500/\mu$l and platelets $\geq 100\,000/\mu$l and complete recovery of non-hematologic toxicities. All toxicities encountered during the study were evaluated according to the National Cancer Institute's Common Toxicity Criteria.

Patients experiencing a delay in chemotherapy of greater than 2 weeks, caused by toxicity, had a one dose level decrease and on the lowest dose level were removed from the study. Response durations were measured from the time of response until there was evidence of progressive disease. The survival duration of patients was measured from the time of entry into the protocol.

## Results

Eighteen women have been entered on the protocol (Table 1. Sixteen are evaluable for response. Two patients were inevaluable for response as they did not receive two cycles of docetaxel. One had an hypersensitivity reaction and bronchospasm immediately after docetaxel. She received only a minimal dose of docetaxel and was evaluable only for toxicity. The other patient was HIV-positive. She developed a lethal flare of pulmonary tuberculosis after the first cycle of docetaxel. The patients had a median age of 42 years (range 30–58) and a median Zubrod performance status of 1 (range 0–2). Eleven (65%) of the 16 evaluable patients received prior radiation therapy and one (6%) received chemotherapy as a radiation sensitizer, 10 (59%) had prior surgery and four (24%) had no prior therapy. Two (13%; 95% CI 0–32%) of the 16 evaluable HIV-nega-

**Table 1.** Patient characteristics

| | |
|---|---|
| No. of patients | 18 |
| evaluable | 16 |
| inevaluable | 2 |
| Age; median (range) | 42 (30–58) |
| Performance status: | |
| 0 | 3 |
| 1 | 6 |
| 2 | 9 |
| Histology | |
| squamous carcinoma | 18 |
| Prior therapy: | |
| none | 4 |
| chemotherapy (radiosensitizer) | 1 |
| irradiation | 11 |
| surgery | 10 |
| Prior chemotherapy: no. of regimens | |
| 0 | 17 |
| 1 | 1 |
| HIV serology | |
| negative | 17 |
| positive | 1 |

**Table 2.** Responses of 16 evaluable patients

| | |
|---|---|
| Partial response | 2 (13%; 95 CI 0–32%) |
| Stable disease | 8 (50%; 95 CI 23–77%) |

**Table 3.** Selected patient major toxicities ($N = 18$)

| | Grade | |
|---|---|---|
| | 3 | 4 |
| Granulocytopenia | 5 | 7 |
| Infection | 0 | 1 |
| Neuropathy sensory | 1 | 0 |
| Neuropathy motor | 1 | 0 |
| Vomiting | 1 | 0 |
| Diarrhea | 1 | 1 |
| Allergic reaction | 1 | 0 |

tive patients had a partial response (Table 2) while eight (50%; 95% CI 23–77%) patients had stable disease and six (37%) progressed. The median time to response was 9 weeks (range 6–12), and the median duration of response was 13.5 weeks (range 6–25). Fourteen of the patients have died. The median progression-free survival was 15 weeks (range 6–33) and the median overall survival was 50 weeks (range 4–112; 95% CI 35–93 weeks). Dose reductions of docetaxel to 75 mg/m$^2$ were required in 10 patients and to 55 mg/m$^2$ in one patient. The granulocytopenia was brief and non-cumulative (data not shown). The median nadir granulocyte count was 400 cells/$\mu$l (range 10–1500) and occurred on day 8. The median nadir platelet count was 195 000/$\mu$l (range 61 000–412 000) and occurred on day 9. The anemia and the thrombocytopenia were not cumulative (data not shown). The infections were mild and infrequent in HIV-negative patients (Table 3) as were the musculoskeletal pain and neuropathy. Nausea and vomiting were mild and manageable. Alopecia was universal. Edema required treatment in three patients.

## Discussion

Despite the moderate activity of platinum, ifosfamide and irinotecan as single agents and the higher activity of polychemotherapy regimens, the survival of patients with cervix cancer has not been prolonged to date relative to treatment with surgery or irradiation without chemotherapy.[19] Accordingly, better treatments for patients with squamous cell cancer of the cervix are needed.

In this phase II trial of docetaxel at a dose of 100 mg/m$^2$ over 1 h every 21 days in patients with advanced or recurrent squamous cell cancer of the uterine cervix we have observed a 13% objective response rate. Furthermore, 50% of the patients had at least a temporary stabilization of their disease with docetaxel and only 37% of these patients progressed prior to the third cycle (6 weeks) of therapy. In preliminary reports of the efficacy of paclitaxel (170 mg/m$^2$ over 24 h or 250 mg/m$^2$ over 3 h) in patients with advanced or recurrent squamous cell cancer of the cervix, objective response rates of 17 and 23% have been reported.[20,21] Clearly the results of the two paclitaxel studies and of this study are similar and confirm taxanes' activity in patients with squamous cell cancer of the cervix. Interestingly, the hematologic toxicity has not been cumulative, as also observed in patients with ovarian cancer treated with paclitaxel.[22] The non-hematologic toxicity has been tolerable in HIV-negative patients.

## Conclusion

Docetaxel has shown activity against squamous cell cancer of the cervix. This study will accrue more patients to better define the response rate, duration of response, progression-free survival, overall survival and toxicity. Likewise, for HIV-positive patients further studies are needed to define docetaxel's efficacy and toxicity. Docetaxel has no cross-resistance with platinum and alkylating agents.

Accordingly, a trial of docetaxel in combination with carboplatin or cisplatin or even ifosfamide would be reasonable. Since this dose schedule is tolerable in patients with previous pelvic irradiation and docetaxel has a radiation sensitizing effect, studies to evaluate the synergism of docetaxel with irradiation should be conducted in patients with cervix cancer.[23,24]

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*(Received 13 February 1996; accepted 14 March 1996)*