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Paclitaxel and Carboplatin Concurrent with Radiotherapy for Primary Cervical Cancer

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Abstract. *Background: Concurrent radiochemotherapy is currently considered the new standard treatment in locally advanced cervical cancer. Patients and Methods: Eight women with cervical cancer stage IB2-IVA were treated with standard radiation therapy in combination with standard carboplatin (AUC=2, once weekly, x 6) and escalating doses of paclitaxel (60 mg/m^2, once weekly, x 4, then x 5 and x 6). Results: At the lowest dose level, four weekly paclitaxel cycles in six patients, three developed grade III diarrhoea and one severe radiation enteritis several weeks after radiotherapy. Two patients did not achieve complete remission and underwent additive salvage hysterectomy. All patients remained free of local recurrence, but one patient had distant metastases after 13 months. The median disease-free survival was 25 months with a median follow-up of 26 months. Conclusion: Standard pelvic radiotherapy in combination with weekly carboplatin and paclitaxel is poorly tolerated due to dose-limiting diarrhoea.*

In the treatment of cervical cancer the addition of cisplatin, alone or in combination with fluorouracil, to standard radiotherapy has resulted in prolonged survival in at least five randomised studies compared to radiotherapy alone (1-5). Combined concurrent treatment is therefore currently considered the new standard treatment in locally advanced cervical cancer (6-8). In order to avoid toxicity and to increase efficacy, a further search for other chemotherapy regimens in this setting is ongoing. Carboplatin has a number of advantages over cisplatin as it does not require admission to prevent nephro- or neurotoxicity and has fewer gastrointestinal side-effects, albeit at the cost of more bone marrow depression (9, 10).

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Paclitaxel has also shown to exert activity in advanced cervical cancer, alone (11, 12) and in combination with platinum analogues (13, 14). The combination of carboplatin and paclitaxel with radiotherapy has shown to be feasible in non-small cell lung cancer or head and neck cancer (15-17). In these studies, local toxicity such as mucositis, oesophagitis and pneumonitis was increased, but this resulted only incidentally in radiation delay, while chemotherapy was seldom delayed for myelotoxicity. A combination of carboplatin and paclitaxel with radiotherapy has not yet been studied in cervical cancer patients. Because this regimen can be given in an outpatient setting, a feasibility study was performed with escalating doses of paclitaxel with carboplatin and concurrent radiotherapy in patients with advanced cervical cancer. The initial dose level was based on the findings in non-small lung cancer and head and neck schemes (15, 17). As the initial number of paclitaxel cycles was limited to four, a slightly higher paclitaxel dose level was used in comparison to the administration scheme by Chen *et al.* (13).

Patients and Methods

This was a feasibility study in which standard radiotherapy was combined with weekly carboplatin and an increasing number of weekly cycles of paclitaxel.

Eligibility criteria. Women with histologically proven FIGO stage IB2-IVA cervical carcinoma, who met the following criteria, were eligible: no prior chemotherapy or pelvic radiotherapy, no concurrent other anti-tumour or investigational therapy; WHO performance status ≤ 2; age > 18 and < 75 years; life expectancy ≥ 3 months; adequate bone marrow (leukocyte count ≥ 3.0 x 10^9/L or platelet count ≥ 100 x 10^9/L); serum bilirubin ≤ 30 μmol/L; serum creatinine > 120 μmol/L and a creatinine clearance ≥ 60 mL/min. Exclusion criteria included patients with enlarged para-aortic lymph nodes on CT or MRI. Patients with active infection, cardiac failure or other serious medical conditions were excluded. The study was approved by the local Medical Ethical Committee and all patients gave written informed consent.

Table I. *Patient characteristics.*

	Number of patients
Total	8
Age, median (range) in years	45 (38 - 69)
WHO performance score	
0	8
Tumour histology	
squamous carcinoma	7
adenocarcinoma	1
Tumour differentiation	
grade 1	5
grade 2	1
grade 3	2
Tumour stage	
IIA	2
IIB	6

Study design and treatment. Standard radiation therapy consisted of 1.8 Gy on days 1 to 5 of each week, for a total of 25 fractions over 5 weeks (total dose 45 Gy), by a 6-15 MeV photon beam four-field technique. Immediately, after completing external radiotherapy, brachytherapy (Caesium 137) 17.5 Gy, repeated after one week, totalling 35 Gy to point A or an external boost to a total dose of 70 Gy was used.

Carboplatin (Paraplatin®; Bristol-Myers Squibb Company, Princeton, NJ, USA) and paclitaxel (Taxol®; Bristol-Myers Squibb Company) were given weekly simultaneously with radiation therapy. Each chemotherapy cycle consisted of carboplatin AUC=2 according to Calvert (18) (carboplatin dose = [creatinine clearance + 25] x AUC) *i.v.* in 250 mL 5% glucose over 30 min and paclitaxel 60 mg/m^2 *i.v.* in 1 L 0.9% NaCl over 1 h, both on the same day every week. To avoid hypersensitivity reactions, dexamethasone 8 mg, clemastine 2 mg and ranitidine 50 mg were administered *i.v.* to all patients prior to initiation of paclitaxel infusion. Carboplatin was given as standard for six cycles. On the first dose level, four cycles of paclitaxel were projected. The number of paclitaxel cycles was then to be escalated to 5 and 6 cycles in cohorts of three patients each.

Dose escalation was based on the toxicity in each cohort; there was no dose escalation within a cohort. Additionally, three patients to a total of six were treated if one or two of the first three patients exhibited dose-limiting toxicity (DLT). If three patients exhibited a DLT, a total of six patients were to be treated at the previous dose level, which was considered to be the maximum tolerated dose (MTD). MTD is defined as the dose level at which DLT in no more than two patients occurred. Toxicity was recorded according to the CTC grading system. DLT were defined as any of the following events: febrile neutropenia, platelets < 25 x 10^9/L requiring platelet transfusion, or CTC grade III non-haematological toxicity, *e.g.* diarrhoea, bladder or skin problems.

Patients went off study in case of tumour progression, unacceptable toxicity or withdrawal of consent. Cervical biopsies were performed 8 to 10 weeks after treatment completion. In case of positive biopsies, an additive hysterectomy was performed.

Treatment modifications. Carboplatin and paclitaxel administration was postponed up to 2 weeks if the platelet count was below 100 x 10^9/L and WBC < 3.0 x 10^9/L at the next cycle. If bone marrow had not recovered, the patient went off study and received the remaining standard radiotherapy. Dose modification was only indicated if myelosuppression induced clinical problems: infection, fever or platelet transfusions. In case of these toxicities, the dose of carboplatin and paclitaxel was reduced to 80%. In case of non-haematological toxicity CTC grade IV, radiotherapy was withheld until recovery. Delays of radiotherapy were avoided as much as possible, as radiotherapy is considered to be the standard treatment.

Results

From January 2000 to March 2002, eight patients were entered in this study (Table I).

Toxicity. In the first cohort, four cycles of paclitaxel, six patients were entered (Table II). One patient had febrile neutropenia after the fourth paclitaxel cycle. In one patient, the last carboplatin cycle was omitted for thrombocytopenia grade II. Another patient had leucopenia grade III without fever and anaemia grade III, for which she received a red blood cell (RBC) transfusion. This patient developed radiation enteritis several weeks after treatment completion.

Three out of the six patients had an episode of diarrhoea grade III. This started after the first cycle in two and after the second cycle in the third patient. After diarrhoea recovery, paclitaxel was not resumed.

In the second cohort of patients, who were to receive 5 cycles of paclitaxel, two patients were entered. Both patients had an episode of diarrhoea grade II, but both completed the projected number of five cycles of paclitaxel. Diarrhoea did not completely respond to loperamide, but recovered after discontinuation of paclitaxel. Bacterial cultures of faeces were negative for pathogens. One patient required a RBC transfusion.

In all, seven patients had mild abdominal pain: grade I in five and grade II in two patients. Other grade II toxicities were fatigue (3 patients), nausea (2 patients), vomiting (1 patient), alopecia (all patients) and bladder urgency (2 patients). Two patients experienced exanthema as a possible reaction to paclitaxel. There were no delays in radiation treatment.

Anti-tumour activity. Two patients with positive cervical loop biopsies after treatment completion underwent salvage hysterectomy and are in complete remission after respectively 13^+ and 27^+ months of follow-up. All patients are free of local recurrence, but one patient had distant metastases after 13 months. Median disease-free survival is 25 months (range, 11 to 37) at a median follow-up of 26 months.

Table II. *Number of paclitaxel and carboplatin cycles planned and actually given and maximum CTC grade or dose-limiting toxicity per patient. RBC = red blood cell, CTC = common toxicity criteria.*

Patient number	Paclitaxel		Carboplatin	RBC transfusion	Neutropenia CTC grade	Diarrhoea CTC grade	Abdominal pain CTC grade
	Planned number of cycles	Actual number of cycles	Actual number of cycles				
1	4	2	6	no	0	III	I
2		4	6	no	0	I	I
3		4	6	no	I	II	I
4		4	6	yes	III	radiation enteritis	II
5		3	6	no	0	III	0
6		2	5	no	0	III	I
7	5	5	5	yes	II	II	II
8		5	6	no	0	II	I

Discussion

The main aim of this study was to evaluate the feasibility of an outpatient regimen combining an escalating number of weekly paclitaxel cycles with standard dose of carboplatin and concurrent radiation therapy. Our study is the first to combine carboplatin and paclitaxel in addition to radiotherapy in cervical cancer. Our results indicate that this combination is not feasible, even at a relatively low paclitaxel dose level, because of dose-limiting diarrhoea.

Studies in several other tumour types have evaluated various paclitaxel-based schedules combined with radiotherapy. In non-small cell lung cancer patients receiving paclitaxel-carboplatin combination with concurrent radiotherapy, oesophagitis grade III-IV was dose-limiting in several studies. Treated with weekly paclitaxel 50 mg/m^2 and carboplatin AUC = 2 over 7 weeks with a total radiation dose of 66 Gy, nine out of 23 patients developed oesophagitis grade III-IV (19). In a similar schedule with weekly paclitaxel 45 mg/m^2 plus carboplatin AUC = 2 and a radiation dose-regimen escalating from 60-74 Gy over 6 weeks, five out of 29 patients experienced oesophagitis grade III (17). In a study with hyperfractionation up to 70 Gy, in combination with weekly paclitaxel 50 mg/m^2 and carboplatin AUC = 2 over 6 weeks, oesophagitis grade III-IV was dose-limiting in 11 out of 43 patients (19). The hyperfractionation study also mentioned 7% CTC grade III and 9% CTC grade IV pulmonary toxicity (20).

Our data suggest that the gastrointestinal tract is the dose-limiting factor for a combination of paclitaxel with pelvic radiotherapy. In the study by Kemp, diarrhoea was observed in three out of 16 patients receiving weekly paclitaxel up to 50 mg/m^2 and cisplatin 50 mg/m^2 every 3 weeks (21). In a previous phase II study, combining a similar dose of carboplatin 300 mg/m^2 on day 1 with 5-fluorouracil 600 mg/m^2/d x 4 as continuous infusion but without paclitaxel, we encountered severe diarrhoea in only two out of 74 patients and in two out of 39 control patients irradiated without chemotherapy, indicating that the addition of paclitaxel to platinum-based chemotherapy will especially induce diarrhoea (22). Other studies observed paclitaxel-induced necrosis of the gastrointestinal mucosa and a higher risk of developing typhlitis and *C. difficile* infection (23, 24). Typhlitis is an inflammatory process of the cecum in granulocytopenic patients, which may occur after paclitaxel. Histopathological changes are cecal thickening and mucosal necrosis with ulceration and dilated blood vessels (25). In our study, only discontinuation of the paclitaxel administration was effective. We considered a further decrease of the paclitaxel dose not worthwhile, as we would probably reach an ineffective dose range for a cytotoxic effect, because 60 mg/m^2 equals a standard dose of 175 mg/m^2 per week.

In conclusion, the study combining radiotherapy with concurrent carboplatin and escalating paclitaxel doses in cervical cancer was aborted for excessive diarrhoea, which occurred even at the lowest paclitaxel dose step.

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