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Original article

Phase I study with weekly cisplatin–paclitaxel and concurrent radiotherapy in patients with carcinoma of the cervix uteri

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Summary

Background. Cisplatin and paclitaxel are active in cervical cancer and both are able to potentiate the effects of radiotherapy. In this study we evaluated the maximum-tolerated dose (MTD) of paclitaxel in combination with a fixed dose of cisplatin when given weekly concurrently with pelvic radiotherapy to patients with carcinoma of the cervix uteri.

Patients and methods: Eighteen patients with cervical cancer were enrolled in this study. Cisplatin (30 mg/m^2) and paclitaxel (starting dose 40 mg/m^2; 5 mg/m^2 escalation per level) were given on day 1 of radiotherapy and then weekly for six times. Radiotherapy was given to the pelvis with a four-field box technique for five days each week. Patients received 65 Gy in 1.8 Gy fractions. Cohorts of three patients were enrolled at each level and three further patients were included if one or two dose-limiting severe adverse events (SAE) were recorded. SAE was defined as grade 3 or 4 nonhematologic toxicity, excluding nausea or vomiting and alopecia, grade 4 neutropenia or thrombocytopenia, and prolonged (> 1 week) neutropenia or thrombocytopenia.

Results: Four levels were studied (paclitaxel 40, 45, 50, 55 mg/m^2) with three, five, four and six patients enrolled, respectively. The MTD of paclitaxel was found at 50 mg/m^2/wk and cisplatin 30 mg/m^2/wk. Diarrhea was the dose-limiting toxicity. Thirteen patients were evaluable for response: seven complete and five partial responses were obtained with an overall response rate of 92.3%.

Conclusions: The MTD of paclitaxel is 50 mg/m^2/wk when associated to cisplatin 30 mg/m^2/wk and concurrent pelvic radiotherapy. Diarrhea is the dose limiting side effect. Preliminary data suggest that concurrent chemoradiotherapy with paclitaxel and cisplatin could be a very active treatment for patients with locally advanced carcinoma of the cervix.

Key words: cervical cancer, chemotherapy, phase I, radiotherapy

Background

Carcinoma of the cervix is one of the most common malignancies in women worldwide. The failure of women to adhere to screening guidelines and of many healthcare providers to recommend screening to their patients makes the proportion of women diagnosed with locally advanced disease even higher. The stage at diagnosis is the best predictor of the prognosis and the cure rates fall sharply with more advanced stage disease [1, 2]. Radiation therapy is considered standard treatment for stage II B, III and IVA cervical cancer [3]. However, as no relevant prognostic improvement has been obtained in recent decades, new strategies, including combined treatment modalities with radiotherapy and chemotherapy [4, 5] have been the subjects of clinical trials. Several phase III studies showed that concurrent chemoradiotherapy with hydroxyurea could improve outcome of patients compared with radiotherapy alone [6–8] or radiotherapy + misonidazole [9]. Based on these trials, hydroxyurea has, in recent years, been considered as the standard chemotherapy treatment concurrent with radiation, although this has not been accepted worldwide.

Cisplatin has been studied in association with radiotherapy since it is the most active agent against cervical cancer and is less myelotoxic than hydroxyurea [10]. Recently, five randomized studies have shown that platinum-based chemotherapy, given concurrently with radiotherapy, prolongs disease free and overall survival of women with locally advanced cervical cancer compared with radiotherapy alone [11–13] or radiotherapy plus hydroxyurea [14, 15].

These impressive results and the availability of new active drugs [16] suggests the study of new combination regimens in this group of patients. Paclitaxel is active in cervical cancer either alone [17] or combined with cisplatin [18, 19]. *In vitro,* paclitaxel potentiates the antitumor activity of ionizing radiation and recruits cells in the most radiosensitive phase of the cell cycle, the G2/M [20, 21]. The combination of weekly paclitaxel with carboplatin [22, 23] or cisplatin [24] along with radiotherapy has been previously studied in head and neck cancer [22] and in lung cancer [23, 24], where it proved to be active.

On these grounds, we started a phase I study in order to evaluate the maximum-tolerated dose of weekly

paclitaxel in combination with cisplatin 30 mg/m^2/ weekly concomitantly with pelvic radiotherapy to patients with carcinoma of the cervix.

Patients and methods

Patients

Women with a histologically proven diagnosis of carcinoma of the uterine cervix, FIGO stage IIB to IVA or with pelvic disease recurrent after surgery were eligible, if they fulfilled the following criteria: aged ≤ 70 years, ECOG performance status ≤ 2, no previous chemotherapy or radiotherapy, leukocytes $\geq 4000/mm^3$, platelets $\geq 100{,}000/mm^3$, serum creatinine < 1.5 mg/dl. All patients were evaluated by clinical examination and hematological and biochemical assessment and were staged with two-view chest X-rays, magnetic resonance or computed tomography of the pelvis, cystoscopy and rectosigmoidoscopy, bone scan and X-ray details of the hot-spots.

The study was approved by the local medical ethics committee and informed consent was sought.

Chemotherapy

Antiemetic premedication with 5-HT_3 antagonists at standard doses was given. All patients received standard antihypersensitivity premedication. Chemotherapy was administered weekly for six weeks, starting on the first day of radiotherapy. Paclitaxel was kindly supplied by Bristol-Myers Squibb Co. Rome, Italy, as a concentrated sterile solution of 6 mg/ml in a 5 ml ampule in 50% polyoxethylated castor oil (Cremophor EL: BASF Hules, Akttengesellschaft, Marl, Germany) and 50% dehydrated alcohol. It was diluted in 500 ml normal saline, administered over a one-hour period, followed by cisplatin, which was also given over one hour. A short-term hyperhydration with 500 ml of normal saline over one hour was given before paclitaxel and post-cisplatin hydratation was performed with 1 l of normal saline given over two hours.

Radiotherapy

Patients received a whole pelvic external irradiation using an X-ray accelerator with 23 MeV photons of energy. The treatment was given at the isocenter using a four-field box technique. The total dose administered was 45 Gy with fractions of 1.8 Gy administered five days a week. The upper edge of the antero-posterior and opposite portals was fixed at L4–L5 interspace, the lateral edges were extended to a 2 cm margin on the pelvic rim and the inferior border was at the inferior border of the obturator foramen; for patients with vaginal involvement it was at the introitus. For lateral fields the anterior margin was placed at the posterior margin of the pubic symphysis bone; the posterior margin was designed to cover 50% of the rectum, or in advanced local tumors, it was extended to the sacral hollow. An additional external irradiation dose of 20 Gy with standard fractionation, was delivered to the gross tumor volume with the same technique.

Study design

This phase I study was designed to define the MTD of weekly paclitaxel when combined with cisplatin 30 mg/m^2 and pelvic radiotherapy. The paclitaxel starting dose was 40 mg/m^2/wk and increments of 5 mg/m^2/wk were planned at each level until severe adverse events (SAE) occurred in three or more out of six patients treated at a given level. SAE was defined as grade 3 or 4 nonhematologic toxicity, excluding nausea or vomiting and alopecia, and grade 4 neutropenia or thrombocytopenia. Chemoradiotherapy was suspended if the neutrophil and platelet counts fell below 1000 and $100{,}000/mm^3$, respectively; treatment was resumed once the counts rose above those levels. In case such neutropenia or thrombocytopenia persisted after a one week delay of chemo-radiotherapy, it was considered as a SAE. If one or two cases of SAE were observed in three patients, three additional patients were treated at the same dose level. The MTD was defined as the dose level before that inducing three or more SAE. In case eligible patients were observed while the evaluation of the last cohort was still ongoing, they could be enrolled at the preceding fully evaluated dose level, but their treatment did not affect the evaluation of the MTD of paclitaxel.

Table 1. Patient characteristics.

		n
Number of patients		18
Age (years)		
Median	58	
Range	42–70	
Histology		
Squamous-cell carcinoma		17
Adenocarcinoma		1
Grade		
1		1
2		4
3		13
Stage of disease		
IIB		7
III		6
Pelvic recurrences		5

Toxicity was evaluated according to WHO criteria [25]. Hematologic and non-hematologic toxicity were evaluated every week. The worst grade toxicity was recorded for each patient. Objective responses were assessed according to WHO criteria [25] two months after the end of chemoradiotherapy. Response evaluation could be done sooner in cases of clinically evident or suspected progression of the disease. Confirmation of response was performed after two further months. Complete response was defined as the disappearance of all sites of disease; partial response as a reduction of at least 50% in the sum of the products calculated for each measurable lesion by multiplying the longest diameter of the lesion by the longest among diameters perpendicular to it, with no appearance of new lesions; stable disease was defined as a reduction lower than 50% or an increase not greater than 25% in the sum of the products, as described above, with no appearance of new lesions; progressive disease was defined as an increase greater than 25% in the sum of the products as described above or the appearance of new lesions. Objective response rate was defined as the proportion of complete + partial response in all patients. Exact 95% confidence limits (CL) are reported (Geigy Scientific Tables).

Results

Between April 1997 and November 1998, 18 women were enrolled in the study (Table 1). Four levels were studied (Table 2): paclitaxel 40 mg/m^2 (level 1), paclitaxel 45 mg/m^2 (level 2), paclitaxel 50 mg/m^2 (level 3), and paclitaxel 55 mg/m^2 (level 4), with three, five, four, and six patients enrolled, respectively per level. SAE were observed in one patient at level 2 (grade 3 thrombocytopenia lasting longer than one week after the fourth week of treatment) and in three patients at level 4, after the fourth (two cases) and fifth week of treatment cycle (one case), consisting of grade 3 diarrhea, associated in one case with grade 4 neutropenia. Thus, the MTD of paclitaxel was defined at 50 mg/m^2/wk. All patients received the whole planned treatment. The four patients who

Table 2. Studied dose levels.

Dose level	Drug doses (mg/m^2)		Number of patients	Dose-limiting severe adverse events
	Cisplatin	Paclitaxel		
1	30	40	3	–
2	30	45	5	1 persisting thrombocytopenia
3	30	50	4	–
4	30	55	6	3 grade 3 diarrhea (in 1 case associated with grade 4 neutropenia)

Table 3. Hematologic toxicity according to WHO grade in 18 patients.

	Level 1 (3 patients)	Level 2 (5 patients)	Level 3 (4 patients)	Level 4 (6 patients)
Leukopenia				
1	1	1	1	3
2	1	3	2	2
3			1	1
Neutropenia				
1	1	4	1	2
2	1	1		3
3			3	
4				1
Thrombocytopenia				
1			1	
2				
3		1		
Anemia				
1	1	3	3	3
2	1	1	1	3
3		1		

Table 4. Non-hematologic toxicity according to WHO grade in 18 patients.

	Level 1 (3 patients)	Level 2 (5 patients)	Level 3 (4 patients)	Level 4 (6 patients)
Pelvic mucositis[a]				
1	2	1	2	2
2	1	2	1	1
Nausea/vomiting				
1	2	3	1	2
2	1	1	1	1
3		1		
Diarrhea				
1	2	1		1
2		2	3	
3				3
Peripheral neurotoxicity				
1	2	3	1	2
2		1		
Cystitis				
1	2	3	1	2
2		1		
Alopecia				
1	1			
2	3	3	2	3
3	1			
Myalgias				
1		1	1	
2	1	1		1

[a] Including proctitis, vaginitis.

experienced SAE remained on treatment at the lower paclitaxel dose level.

Hematologic toxicity was mild overall (Table 3). Grade 3–4 neutropenia was recorded in four cases (three at level 3 and one at level 4); in no case was febrile neutropenia recorded; one case of grade 3 thrombocytopenia was observed at level 2; grade 3 anemia occurred in one patient.

Nausea and vomiting was the most frequent non-hematologic side effect (Table 4). Neurotoxicity was mild but frequent, while grade 1–2 mucositis (vaginitis, proctitis or both) was reported in 66% of the patients. No hypersensitivity reaction was observed. No cardiotoxic events occurred. Grade 3 diarrhea was the only severe and dose-limiting non-hematologic toxicity, recorded in three patients at level 4. Diarrhea was frequent, being recorded in 66% of the cases: the degree of diarrhea increased by level, being dose-limiting at level 4. Other frequent gastrointestinal symptoms were dyspepsia and abdominal pain that where recorded in 50% of the cases. No relevant long-term toxicity was recorded during follow-up of patients.

Thirteen patients had measurable disease and were evaluable for response. Objective responses were recorded in 12 patients (92.3%, 95% CI: 64.0–99.8); 7 (53.8%) achieved a complete response and 5 (33.4%) a partial response. All responses were radiologically confirmed after two months.

Discussion

In the present study we looked for the MTD of weekly paclitaxel associated with 30 mg/m^2 of cisplatin given concurrently with pelvic radiotherapy in patients with locally advanced cervical cancer. Diarrhea was the dose limiting toxicity at paclitaxel dose of 55 mg/m^2. The MTD, to be used in further phase II studies, was found at level 3 (cisplatin 30 mg/m^2 plus paclitaxel 50 mg/m^2). Hematologic toxicity was overall mild; neutropenia was the most frequently recorded.

The possible mechanisms of interaction between chemotherapy and radiation include the action on different tumor cell subpopulations, cycle-related cell mechanisms (recruitment in G1, synchronization), and the prevention of the emergence of drug and radiation resistance [4, 5]. Concurrent chemoradiotherapy, if synergistic, might produce a therapeutic advantage, without prolonging overall treatment time, as compared to a sequential approach. At present, cisplatin is considered the single most active cytotoxic agent in cervical cancer [16, 26]. This drug inhibits the repair of sublethal damage from radiation [27] and has a synergistic effect with radiotherapy [28]. Some randomized phase III studies have recently demonstrated that cisplatin-based chemo-

therapy given concurrently with radiotherapy improves the rates of survival and progression-free survival of cervical cancer patients [11–15]. Namely, Rose et al. [14] randomized 526 women with stage IIB, III, or IV cervical cancer to receive radiotherapy concomitantly with 1 of 3 chemotherapy regimens: weekly cisplatin, 2 courses of cisplatin–hydroxyurea–fluorouracil, and twice weekly hydroxyurea. The progression-free survival rates were significantly higher in the two groups that received cisplatin, with less toxicity in the one with cisplatin alone. On the basis of these results, weekly cisplatin was recommended as the standard drug for radiotherapy and chemotherapy for locally advanced cervical cancer.

New combinations of chemotherapy given concurrently with radiotherapy can further improve the prognosis of these patients. Paclitaxel was chosen for the present study because of its activity against cervical cancer [16–19] and its favorable interactions with radiation [20, 21].

Weekly paclitaxel combined with cisplatin or carboplatin and given concurrently with radiotherapy has been previously studied in lung cancer and head and neck cancer where it proved to be active and safe [22–24].The doses reached in our trial are similar to those found in these studies with similar toxicity profiles. A different schedule of weekly paclitaxel and cisplatin has been studied by Chen et al. [29]. In a phase I study the authors gave up to 50 mg/m^2 paclitaxel weekly combined with 50 mg/m^2 cisplatin every three weeks; similar to our study, gastrointestinal toxicity was the main side effect.

Although the evaluation of treatment activity was not the primary aim of our study, we found an overall response rate higher than 90%, that suggests a clinically relevant activity of this combination treatment.

We accept that, in view of the toxicity found, there could be room to further increase cisplatin dose. However, in the context of chemo-radiotherapy every efforts should be done to avoid unnecessary prolongation of radiotherapy that would negatively affect the outcome of patients, as largely recognized.

On the basis of these results, the weekly combination of cisplatin 30 mg/m^2 plus paclitaxel 50 mg/m^2 plus concurrent radiotherapy should be considered for further phase II or even phase III studies in comparison with cisplatin alone or other cisplatin-based chemotherapy.

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