Chemoradiation with gemcitabine for cervical cancer in patients with renal failure

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The prognosis of cervical cancer patients with renal failure secondary to obstructive uropathy is poor. Our objective was to analyze our experience in the management with chemoradiation of untreated cervical cancer patients complicated by obstructive nephropathy and kidney dysfunction. Untreated patients with cervical cancer and renal failure as manifested by raised serum creatinine were treated with pelvic radiotherapy concurrently with weekly gemcitabine at 300 mg/m^2. Response, toxicity and renal function pre- and post-therapy were evaluated. Eight FIGO stage IIIB and one IVB patients were treated. Pre-treatment serum creatinine ranged from 1.6 to 18.5 mg/100 ml (median 3.3, mean 6.8) and creatinine clearance varied from 4 to 57 mg/ml/min (median 17, mean 22.1). Four patients had a percutaneous nephrostomy placed and four patients had symptoms from kidney failure. All patient completed chemoradiation. Most patients had grade 3 leukopenia and neutropenia. Dermatitis, colitis and proctitis were common. All patients had improvement in creatinine clearance (pre-therapy 22.78, post-therapy 54.3 mg/ml/min) ($p=0.0058$) and all but one normalized serum creatinine. Eight (89%) of nine patients achieved complete response and one patient had persistence. At a median follow-up of 11 months (range 6–14), all patients are alive, one with pelvic and another with systemic disease. Ureteral obstruction causing any degree of renal insufficiency should not be a contraindication to receive chemoradiation to attempt cure. In this setting where cisplatin-based therapy is contraindicated, the use of gemcitabine may be considered. *Anti-Cancer Drugs* **15:761–766 © 2004 Lippincott Williams & Wilkins.**

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Introduction

Cervical carcinoma is the most frequent cause of death by cancer in women from developing countries [1]. For early stages of the disease, radiation and surgery are equally effective treatment modalities; however, the prognosis of patients with locally advanced disease is still unsatisfactory despite the 12% absolute benefit on 5-year survival from concomitant cisplatin-based chemoradiation, which is now the current standard of treatment [2].

Ureteral obstruction by the disease spreading to parametria and/or to the bladder is not an uncommon condition in patients with locally advanced disease. A number of clinicopathological characteristics have been studied as prognostic factors in cervical cancer. In this regard, the status of the renal function is a highly significant factor predicting survival. In FIGO stage IIIB patients with no ureteral obstruction the 5-year survival is 47%, which shortens to 29% when uni- or bilateral hydronephrosis is present, but in the presence of renal failure no patients survive beyond 18 months, therefore ureteral obstruction and kidney failure are independent prognostic factors for survival [3,4].

Patients with obstructive renal failure, in addition to having a dismal outcome, face the medical conditions derived from the poor renal function, which may interfere with the delivery of chemotherapy and or radiation. The management of newly diagnosed cervical cancer patients presenting renal insufficiency is challenging and varies among cancer centers. Several authors report on the use of percutaneous nephrostomy or other forms of surgical diversion as a way to relieve the obstruction and improve the function of the kidney. However, the value of this approach on quality of life improvement or prolongation of survival is poor. In fact, several studies show that patients submitted to such procedure frequently have longer hospital stays, poor quality of life and a median survival time of only 4 months [5–8].

Despite that patients with renal failure have a poor prognosis, some of those who respond to pelvic radiation alone can achieve normal serum creatinine levels, and the primary disease can thereafter be potentially controlled [9,10]. Because of the demonstrated benefit of chemotherapy administered during radiation, we thought that patients with renal obstructive disease and compromised

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renal function fit enough to receive standard pelvic radiation, should also receive a radiosensitizer.

Cisplatin is contraindicated in patients with renal failure. Likewise, carboplatin, though less nephrotoxic than the parental compound, is not an option in renal failure patients despite that it is successfully administered in patients felt to have subclinical renal dysfunction [11]. Thus, we decided to use gemcitabine because of its potent radiosensitizing properties *in vitro* against cervical cancer cell lines [12] and its efficacy on cervical cancer patients, either alone or in combination with cisplatin [13–15]. More importantly, the Cancer and Leukemia Group B has performed a phase I pharmacokinetic trial of this drug in patients with liver and kidney failure, coming to the conclusion that gemcitabine shows no apparent pharmacokinetic differences compared to historical controls; however, patients with abnormal levels of creatinine seemed to have increased sensitivity to gemcitabine [16]. Based on that, and despite of the potential increased toxicity to gemcitabine we could encounter, we decided to use gemcitabine concurrent with radiation in cervical cancer patients with renal dysfunction.

Patients and methods

Untreated patients with a histological diagnosis of cervical cancer and compromised renal function as manifested by raised serum creatinine were included in this analysis. Clinical staging was performed without anesthesia, and patients underwent blood counts, serum chemistry, i.v. pyelography, cystoscopy and renal gammagraphy. Patients with hemoglobin less than 10 g/dl were transfused to achieve at least 10 g/dl. The status of para-aortic lymph nodes was assessed with a computed tomography scan.

Radiation

Patients received external beam radiation using ^{60}Co or linear accelerator equipment with minimum photon-beam energy of 4 MeV at a target or skin source distance of 80 cm to the whole pelvis for a total dose of 50 Gy (5 weeks, 2 Gy fractions from Monday to Friday). This was followed by one or two intracavitary cesium applications 2 weeks after finishing external radiation. The planned total doses to points A and B were a minimum of 85 and 55 Gy, respectively. Patients were treated with the four-field box technique as follows. The irradiated volume was to include the whole uterus, the paracervical, parametrial and uterosacral regions, as well as the external iliac, hypogastric, and obturator lymph nodes. Minimum margins were the upper margin of L5 (superiorly), the midportion of the obturator foramen or the lowest extension of the disease (inferiorly), and 1 cm beyond the lateral margins of the bony pelvis and its widest plane (laterally). For the lateral fields, the anterior margin was the anterior edge of the symphysis or 3 cm in front of the sacral promontory. The posterior margin was the S2–S3 interspace.

Chemotherapy

Gemcitabine was administered weekly for 6 weeks during external radiation, beginning the first day of radiation, and was administered by a peripheral vein in an outpatient setting (at least patients were in hospital because of their medical conditions derived from the renal insufficiency) at a dose of 300 mg/m^2. A total of six weekly doses was administered. No dose modification was allowed, but a dose was delayed for 1–2 weeks with any grade 3 hematological or not hematological toxicity, whereas radiation was held for 1 week with any grade 4 toxicity. Gemcitabine was administered in 500 ml of 0.9 or 0.45% normal saline solution over 30 min. Patients received 8 mg of ondansetron to prevent emesis. Medical management of uremic syndrome included general and specific measures such as water restriction, diet modification and sometimes diuretics. Hemodialysis or peritoneal dialysis were not employed.

Evaluation of response

Response to chemoradiation was evaluated at the third month after treatment. Complete response was registered when no clinical and cytological evidence of disease existed. Persistence or progression was registered as no complete response. Pre- and post-therapy creatinine clearance was calculated with the Cockcroft and Gault formula.

Evaluation of toxicity

The toxicity to chemoradiation was evaluated according to the NCI Common Criteria and presented as toxicity per patient.

Results

Characteristics of patients

From July 2002 to May 2003, a total of nine previously untreated cervical cancer patients with renal dysfunction was treated at our Institution. The clinical characteristics of patients are shown in Table 1. The mean age was 51 years; all patients had squamous tumors. All but one

Table 1 Patient characteristics

No.	9
Age (median)	51 (30–76)
Stage	
IIIB[a]	8
IVB	1
Histology	
squamous	9 (100%)
hemoglobin (median)	9.5 (7.6–12.1)
Performance status (WHO)	
1	5 (55%)
2	4 (45%)

[a]One IIIB patient had positive para-aortic lymph nodes. The staging as IVB was because of inguinal lymph nodes.

Table 2 Status of renal function before treatment

Patient	Stage	Serum creatinine	Calculated creatinine clearance	Renal gammagraphy	Renal ultrasound	Intravenous urography	Percutaneous nephrostomy	Symptoms
1	IIIB	18.5	5	rGF 32 lGF 31	bil H	bil E	yes	yes
2	IIIB	2.0	27	rGF 52 lGF 0	bil H	left E	no	no
3	IVB	7.8	6	rGF 54 lGF 35	bil H	ND	yes	no
4	IIIB	18.4	4	rGF 27 lGF 12	bil H	ND	yes	yes
5	IIIB	1.6	43	rGF 0 lGF 102	bil H	right E	no	no
6	IIIB	5	31	rGF 62 lGF 59	bil H	N	no	yes
7	IIIB	3.2	17	rGF 42 lGF 22	left H	ND	yes	no
8	IIIB	1.8	57	rGF 61 lGF 22	right H	left E	no	no
9	IIIB	3.3	15	lGR 29 rGF 29	ND	ND	no	yes

H: Hydronephrosis, E: renal exclusion.

Table 3 Treatment

No. of patients	9 (100%)
Completed external and intracavitary radiation	9 (100%)
Received gemcitabine	9 (100%)
6 applications	4 (45%)
5 applications	5 (55%)
Mean dose to point A (Gy)	83.7 (79.0–91.7)
Mean dose to point B (Gy)	67.4 (58.8–65.0)
Treatment time (days)	45.2 (34–59)

The treatment to the patient with para-aortic disease is not included in this table.

Table 4 Toxicity to chemoradiation expressed per patient (nine patients)

Toxicity	Grades				
	0	1	2	3	4
Nausea/vomiting	0	4	3	2	0
Fatigue	1	4	4	0	0
Leukopenia	0	0	1	7	1
Neutropenia	0	0	3	6	0
Thrombocytopenia	7	1	0	1	0
Febrile neutropenia	7	0	0	2	0
Infection[a]	5	0	2	2	0
Anemia	0	5	3	1	0
Dermatitis	0	6	1	2	0
Colitis	3	0	5	1	0
Proctitis	2	4	2	1	0
Dysuria	3	5	1	0	0

[a]Urinary infection in the four patients with percutaneous nephrostomy.

patient were FIGO stage IIIB (one these also had para-aortic lymph nodes) and one patient had an IVB stage due to the presence of inguinal lymph nodes. Patients had a WHO status performance of 1 or 2 and the mean hemoglobin concentration pretreatment was 9.5 g/dl.

Pretreatment status of renal function

Table 2 shows that all patients presented elevation of serum creatinine which ranged from 1.6 to 18.5 mg/100 ml (median 3.3, mean 6.8), whereas the creatinine clearance varied from 4 to 57 mg/ml/min, with a median of 17 and a mean of 22.1. The eight cases evaluated by renal ultrasound and/or pyelography had uni- or bilateral hydronephrosis. Four patients had clinical manifestations characterized by edema (four cases), pleural effusion (one case), pulmonary rales (one case) and nausea/vomiting (four cases). The two patients with higher azootemia presented hyperkalemia, hypocalcemia and hyperfosfatemia, and required hospitalization. In four patients a percutaneous nephrostomy was placed. In the two with creatinine of 18.2 and 18.5 mg/dl the nephrostomy was placed within the first week of beginning chemoradiation; in the patient with creatinine of 7.8 mg/dl the nephrostomy was placed before chemoradiation began, hence her creatinine level at starting therapy was 1.5 mg/dl. Finally, in the patient with creatinine of 3.2 mg, the nephrostomy was performed before she came to our institution and started chemoradiation at that level of creatinine.

Chemoradiation

Table 3 shows that the nine patients received both external beam and brachytherapy. Four patients had the six planned courses of concurrent chemotherapy administered whereas five patients only received five applications. The mean dose to points A and B were 83.7 (79.0–91.7) and 67.4 Gy (58.8–65.0), respectively. External radiation was completed in 45.2 (34–59) days. The patient with para-aortic lymph nodes also received chemoradiation to the para-aortic field delivering 45 Gy in 1.8-Gy fractions with concurrent weekly gemcitabine at 200 mg/m^2.

Toxicity

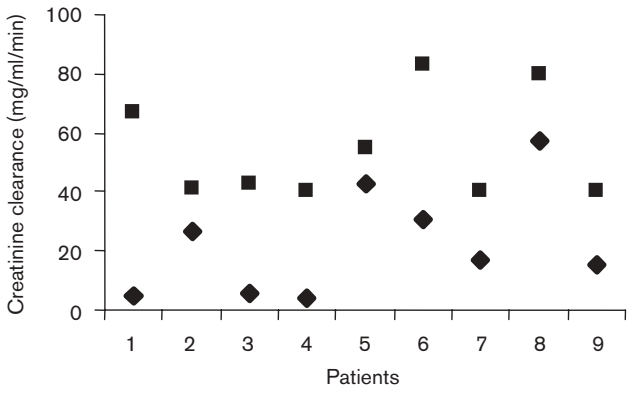
A total of 49 weekly applications of gemcitabine were administered to nine patients. Gemcitabine was well tolerated. The pattern of toxicity is shown in Table 4.

Nausea/vomiting was present in all nine patients and in two cases it was grade 3, and all but one patient complained of mild to moderate fatigue. Hematological toxicity was common and severe. All patients presented leukopenia and neutropenia, being grade 3 in the majority; however, only one case of leukopenia grade 4 was seen. Anemia was also frequent, although grade 3 only in one patient, whereas grade 3 thrombocytopenia was seen in a single patient. Only two patients presented grade 3 febrile neutropenia, but the four patients with percutaneous nephrostomy had at least one episode of urinary infection. All patients presented dermatitis, being grade 3 in two cases. Colitis and proctitis were common, being severe in two cases. Mild to moderate dysuria most probably related to cystitis was commonly seen. With regard to late toxicity, a single patient presented grade 2 small/large bowel toxicity according to the RTOG/EORTC Late Radiation Morbidity Scoring Schema.

Post-treatment renal function

After treatment, there was an improvement in the renal function in all patients as evaluated by serum creatinine and calculated creatinine clearance. All patients had return to normal or near-normal serum creatinine levels. Only, one patient persisted with abnormal creatinine (pre-treatment 3.2 mg; post-treatment 2.1 mg; normal value up to 1.2 mg). As evaluated by calculated creatinine clearance, there was a statistically significant increase in values post-treatment. The mean value before therapy was 22.78 mg/ml/min, which increased to 54.3 mg/ml/min (Wilcoxon test, $p = 0.0058$) after treatment (Fig. 1). With regard to the patients who had percutaneous nephrostomy, the patient with 18.5 mg creatinine had accidentally had her catheter removed during the fifth week of chemoradiation. At that time her creatinine was normal, hence she was left without the drain. The patient with 18.2 mg currently has a double J stent which was placed after treatment. The third patient with nephrostomy that started treatment with a creatinine of 1.5 mg/100 ml is the one with persistence of pelvic disease; she continues with the nephrostomy. Finally, the fourth patient also continues with her double J stent in place.

Fig. 1



Renal function outcome. All patients had an improvement of the creatinine clearance after therapy. Diamonds = pre-treatment. Squares = post-treatment.

Response and current status

With regard to the response to treatment, eight (89%) of nine patients achieved complete responses and one patient had persistence of the pelvic disease. This later patient was the one staged IVB because of inguinal lymph nodes and is currently alive receiving palliative care. The patient staged IIIB that had retroperitoneal lymph nodes achieved a complete response in both pelvic and para-aortic disease, but progressed within the first 6 months after treatment with lung metastases. She is currently receiving palliative systemic chemotherapy. At a median follow-up of 11 months (6–14), all patients are alive, one with pelvic and another with systemic disease.

Discussion

According to the literature, 'cure' is a hope but not a realistic expectation for untreated patients with locally advanced cervical cancer who present at diagnosis with obstructive uropathy and renal failure. First, it should be recognized that hydronephrosis is common, as this condition defines patients as stage IIIB and may be present in around a third of stage IIIB patients [4]. However renal failure derived from the obstructive uropathy is far less common in newly diagnosed patients. Second, there exists no consensus as to whether these patients should receive just palliative care including or not urinary diversion or any form of dialysis, or should be treated with pelvic radiation in a curative attempt plus medical or surgical management of renal failure.

Regardless of the presence of kidney failure, the treatment of stage IIIB patients has special problems for the radiation oncologist, mostly derived from large tumor volume, extension to the pelvic sidewall and likelihood of regional metastases. Accordingly, 5-year survival reported in different series for IIIB patients ranges from 30 to 50% when treated with radiation alone [17–21]. More recently, with the use of concurrent cisplatin-based chemoradiation, the 5-year survival has improved by 12% according to a meta-analysis [22]. Thus, currently all cervical cancer patients in whom radiation is indicated must receive chemotherapy concurrent to radiation. Unfortunately, the subset of patients who already present renal dysfunction may not get the benefit of chemoradiation, because they may receive only palliative therapy or if treated with a curative attempt may not receive cisplatin because of its nephrotoxicity.

New agents such as gemcitabine, paclitaxel, topotecan and irinotecan have recently been evaluated as

radiosensitizers in cervical cancer patients [14,23–25]. Among these, gemcitabine has received considerable attention in the light of its potent radiosensitizer properties and promising results in patients with cervical cancer [26]. Because this agent has been proven safe in patients with renal failure [16] we began to use this agent on a routine basis for those patients with any degree of renal failure associated with obstructive disease and fit to receive radiation in a curative attempt.

The results of this clinical experience demonstrate that chemoradiation is a safe and effective alternative of management for newly diagnosed patients with cervical carcinoma and renal dysfunction as a consequence of obstructive disease. It is remarkable that we have obtained an excellent local control rate, including a patient who also presented para-aortic disease which was treated with chemoradiation to para-aortic nodes.

This is the first experience reported on the use of chemoradiation in this subset of patients. The results reported in series of patients with this condition that received radiation are poor. Meyer *et al.* reported 19 untreated patients with renal obstructive disease and renal failure in whom a urinary diversion was placed before definitive treatment with radiation. Eight of these could not complete the planned treatment and had a median survival of 37 days, whereas the 11 patients that completed treatment with radiation survived 9.8 months (2 months to 4.8 years) [27]. In another series of 18 untreated patients with cervical cancer having oliguria and obstructive renal failure, 13 could receive irradiation and achieved a mean survival of 16.9 months. On the contrary, those who were not treated only survived on average 25.6 days [8]. Similar data were reported by Carter *et al.* on 35 patients with gynecological cancer (most cervical) who underwent percutaneous urinary diversion. Of these, the previously untreated patients who received treatment had a median survival of only 7 months [28].

Our results strongly suggest that chemoradiation may help to control pelvic disease also in the patient population with affected renal function. It remains to be determined, however, what the role is of urinary diversion as an adjunct to the management of these patients. In all the cases there was a re-establishment of renal function as reflected by the normal or near-normal values of serum creatinine achieved. Taylor *et al.* analyzed the outcome of patients who received definitive anti-tumor treatment according to the management employed for the renal failure. They observed no differences between them; those medically treated had a median survival of 13.8 months, compared to 16.2 for the surgically derived. Interestingly, the recovery of renal function post-treatment was similar regardless of the medical or surgical management [8], which is in agreement with our data. In our cases, we observed a lowering in creatinine levels within the first week of chemoradiation in all the patients, but unfortunately our data do not allow establishing the role of the medical management, as the two cases with higher levels of creatinine had surgical diversion. It is known that in this context, surgically diversion is effective in re-establishing renal function [7,10,28,29]; however, our data and those from Taylor *et al.* suggest that such a procedure may not be strictly needed as they observed spontaneous resolution of oliguria on day 11.5 on average in patients medically managed [8]. Due to these observations, we no longer plan to offer surgical diversion to our patients unless they continue oliguric after 2 weeks of initiated radiation and/or their clinical condition worsens. This may avoid the repetitive infections associated with the urinary diversion which may compromise the delivery of chemoradiation.

Non-cisplatin regimens of radiosensitizing in cervical cancer are limited. Aside from gemcitabine, the most used agent has been 5-fluorouracil which, however, when used alone with standard or hyperfractionated radiation showed no better results as compared to radiation alone [30]. Gemcitabine concurrent with radiation is a highly active and well-tolerated treatment. Pattaranutaporn *et al.*, using 5 weekly applications of gemcitabine at 300 mg/m^2, during standard pelvic radiation reported a complete response rate of 89% in 19 FIGO stage IIIB patients, which is approximately identical to our results (eight out of nine achieved complete responses). However, as we predicted from the data reported in patients with renal dysfunction treated with gemcitabine [16], we clearly observed higher hematological and non-hematological toxicity in our patients. Table 4 shows that leukopenia and neutropenia grade 3 and 4 were observed in more than two-thirds of patients; likewise, we observed at least one patient with grade 3 having almost all the remaining toxicities except for fatigue and dysuria. Toxicity of such degree was rare or non-existent in the reported phase II study of gemcitabine [14]. Increased toxicity to gemcitabine was reported in patients with renal dysfunction which could not be explained by pharmacokinetics [16]. Instead, it seems that renal alterations could by an unknown mechanism sensitize the patient to the toxic effects of gemcitabine. Nevertheless, toxicity was manageable and we feel that the benefit on disease control outweighs its toxicity.

Our results allow us to conclude that ureteral obstruction causing any degree of renal insufficiency should not be a contraindication to receive chemoradiation to attempt cure and that gemcitabine is a good option for radiosensitization. However, a larger phase II study is needed to confirm the efficacy and safety of chemoradiation with gemcitabine in this setting, as well as to prospectively investigate the role of surgical diversion within this treatment approach.

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