Concurrent chemoradiation with carboplatin for elderly, diabetic and hypertensive patients with locally advanced cervical cancer

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Summary

Introduction: Chemoradiation based on cisplatin is the standard treatment of locally advanced cervical cancer, however, a subset of patients are either elderly and/or have comorbidities such as diabetes and hypertension. These conditions may compromise the administration of cisplatin. We report our Institution experience with weekly carboplatin as a radiosensitizer for the management of this subset of patients. *Patients and Methods:* We reviewed the files of 59 patients with locally advanced cervical cancer who were treated with primary chemoradiation with weekly carboplatin. Response rate, toxicity and survival were analyzed. *Results:* Mean age was 62 years (range, 36-83 years). The majority of cases were squamous cell carcinoma (88.14%), and distribution according to FIGO Stage was IB2 8.4%, IIA 13.5%, IIB 52.5%, IIIA 3.3% and IIIB 18.6%; Overall, 100% and 91% of patients completed external beam and intracavitary therapy. Seventy-nine percent received from five to six planned cycles of weekly carboplatin. Complete responses were achieved in 49 (83.05 %) patients, whereas ten patients (16.95%) had either persistent or progressive disease. The most common toxicities were grades 1 and 2 hematological and gastrointestinal. At median follow-up (20 months; range 2-48 months), 16 patients (32.65%) have relapsed. Estimated 30-month overall survival is 63%. *Conclusions:* Weekly carboplatin concurrent with pelvic radiation is well tolerated in patients with locally advanced carcinoma of the cervix who are older than 70 years and/or have diabetes mellitus and/or high blood pressure, however, the apparently slighty lower survival observed cautions against its routine use.

Key words: Chemoradiation; Cervical cancer; Carboplatin.

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 [2], 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 [3]. Data from the GOG 120 study [4] shows that weekly cisplatin at 40 mg/m^2 for six applications is equally effective yet less toxic than the combination of cisplatin-5-fluorouracil. Thus, weekly cisplatin is commonly employed as a radiosensitizer in cervical carcinoma patients.

Cancer is a disease of aging, with a steep increase in cancer cases after the age of 60 years. Cervical cancer has always been known as a neoplasia that affects women in middle-age, however due to the alteration in the demographics of cancer because of the aging in our societies, more and more often we are treating elderly patients with this neoplasia who may have age-related changes in pharmacokinetics and pharmacodynamics of antineoplastic therapy which may result in increased toxicity. For instance, renal excretion is affected by a gradual decline in function with age. There is a decrease in the glomerular filtration rate [GFR] by approximately 1 ml/min for every year over the age of 40. The reduction in GFR is not reflected by an increase in serum creatinine because of the simultaneous loss of muscle mass. [5, 6].

Diabetes mellitus and hypertension are both highly prevalent and increasing diseases in the general population [7, 8]. It is considered that 20-30% of patients with diabetes will develop diabetic nephropathy. The progressive stages in the natural history of diabetic nephropathy are glomerular hyperfiltration, microalbuminuria, hypertension, macroalbuminuria and after seven to ten years of persistent proteinuria, an increase of serum creatinine and end-stage renal disease start [9]. Hypertensive nephropathy appears as a complication of persistent high blood pressure which leads to vasoconstriction and a progressive decrease of the renal plasmatic flow which provokes a decrease of the renal mass due to ischemia and could end in renal failure [10].

Carboplatin is less nephrotoxic and emetogenic than cisplatin although it is more myelosuppressive [11, 12]. In cervical cancer, preclinical and clinical studies demonstrate that it is equally effective yet better tolerated than cisplatin [13-18]. In addition, it is a radiosensitizer [19, 20]. We previously reported that the recommended dose of carboplatin to be used weekly with radiation was 133 mg/m^2 (total of 800 mg/m^2) [21]. Since that study we adopted chemoradiation with carboplatin as routine treatment in our Institution for patients with locally advanced cervical cancer, patients with high-risk conditions to

Revised manuscript accepted for publication December 31, 2007

develop renal dysfunction by cisplatin, such as diabetes mellitus, high blood pressure and/or ≥ 70 years old. Hence, we wanted to analyze our results of treatment with carboplatin chemoradiation as routine management in this specific subgroup of cervical cancer patients.

Materials and Methods

Patients. We conducted a retrospective review of 59 consecutive newly diagnosed and previously untreated patients who received radiotherapy and concurrent carboplatin at the INCAN between January 2002 and June 2006. All patients had a histological diagnosis of cervical carcinoma and were staged according to the FIGO classification using the standard pretreatment workup (pelvic examination without anesthesia). Carboplatin was used for sensitization if patients had at least one of the following criteria: age older than 70 years, diabetes mellitus and/or high blood pressure. As this was a retrospective review on patients treated on a routine basis, no ethical approval was required by our Institution.

Treatment. Patients received external beam radiation (EBRT) using megavoltage machines (Co^{60} or lineal accelerator equipment) with a minimum photon-beam energy of 2.25 MV with an isocenter technique to the whole pelvis for a total dose of 50 Gy (5 weeks, 2 Gy fractions from Monday to Friday) followed by one or two intracavitary cesium (low-dose rate) applications within two weeks of finishing EBRT. The planned total dose to point A was at least 85 Gy. Patients were treated with the conventional 4-field box technique. Irradiated volume was to include the whole uterus, paracervical, parametrial, and uterosacral regions, as well as external iliac, hypogastric, and obturator lymph nodes. Carboplatin was administered for six weeks during external radiation, beginning on the first day of radiation. Carboplatin infusion was used at a dose of 133 mg/m^2 and administered via a peripheral vein to patients in an outpatient setting as follows: carboplatin diluted in 500 ml of glucose solution at 5% for 60 min intravenously. Intravenous ondansetron (8 mg) and dexametasone (8 mg) were employed as antiemetic prophylaxis. Carboplatin (but no radiation) was withheld in any case of grade 3 toxicity until the toxicity regressed to any grade < 3; in patients with grade 3 toxicity that persisted > 2 weeks, chemotherapy was no longer administered. Radiation was only stopped in cases of grade 4 hematological or non-hematological toxicity until toxicity resolved to at least grade 3.

Response evaluation. Response to chemoradiation was clinically and cytologically evaluated at the third month after ending treatment. Complete response was registered when no clinical and cytological disease evidence existed; all other cases were registered as persistent or progressive disease. Persistent disease was considered with any less-than-complete response, and progression was defined as local or systemic: local existed when there was an increase > 25% in initial lesion size, and systemic was considered with the appearance of new lesions irrespective of local response.

Follow-up. Upon treatment completion, patients were evaluated every three months for the first year, every four months during the second year, every six months during the third year, and annually thereafter. At each visit, a physical and pelvic examination, blood counts, clinical chemistry, and chest X-rays were performed. Computed tomography (CT) scan, ultrasound (US), and other imaging studies were conducted when appropriate. Suspected cases of persistent or recurrent disease were confirmed by biopsy whenever possible.

Table 1. — *Clinical characteristics.*

Characteristics	Number	(%)	Range
Mean age (years)	59		36-83
High blood pressure	22	(37)	
Diabetes mellitus	28	(47)	
Both	9		
Age ≥ 70	9	(15)	
Mean hemoglobin at diagnosis		13.84	8.1-16.8
Stage			
IB2	5	(8.4)	
IIA	8	(13.5)	
IIB	31	(52.5)	
IIIA	2	(3.3)	
IIIB	11	(18.6)	
IVA	2	(3.3)	
Histology			
Squamous	52	(88.14)	
Adenocarcinoma	6	(10.17)	
Others	1	(1.69)	

Table 2. — *Chemotherapy delivered.*

Weekly cycles	Number of patients %
6	21 (35.6)
5	25 (42.3)
4	8 (13.5)
3	4 (6.7)
2	1 (1.67)

Statistical analysis. Overall survival was analyzed on an intention-to-treat basis and was registered from date of diagnosis to date of death or date of last visit. The curve was constructed using the Kaplan-Meier method.

Results

Patient characteristics. A total of 59 patients were analyzed. Patient clinical characteristics are shown in Table 1. The majority of cases were squamous cell carcinoma (88.14 %), and distribution according to FIGO stage was IB2 8.4%, IIA 13.5%, IIB 52.5%, IIIA 3.3% and IIIB 18.6%; there were only two IVA cases (3.3%). Mean hemoglobin at diagnosis was 13.8 g/dl with ranges between 8.1 and 16.8. Mean age was 62 years (range, 36-83 years). Twenty-two (37%) patients had high blood pressure, 28 (47%) were diabetic (9 of these 50 patients had both conditions) and nine (15%) patients were aged > 70.

Treatment. Mean dose of EBRT was 50.5 which was delivered in a mean of 39 days (S.D. 6.8). Brachytherapy insertions to complete the planned dose were applied once in 54 patients (57.63%) and twice in 20 (33.90%). Overall, 91.53% of patients completed both phases. Five (8.47%) patients did not receive brachytherapy. With regard to chemotherapy, 78% of patients received from five to six planned cycles of weekly carboplatin, 25 patients (42.3%) and 21 patients (35.6%), respectively (Table 2). One (1.69%) and four patients (6.7%) could only receive two and three applications, respectively, while eight (13.5%) patients received four applications of carboplatin.

Table 3. — *Acute common toxicity criteria of the National Cancer Institute (CTC NCI) version 2 criteria (59 patients).*

Grade	0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)
Fatigue	2 (3.4)	7 (11.8)	50 (84.7)	0 (0)	0 (0)
Fever	59 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Anorexia	58 (98.3)	1 (1.7)	0 (0)	0 (0)	0 (0)
Diarrhea	22 (21)	40 (38)	0 (0)	0 (0)	0 (0)
Proctitis	56 (94.9)	2 (3.4)	1 (1.7)	0 (0)	0 (0)
Nausea	7 (11.9)	17 (28.8)	35 (59.3)	0 (0)	0 (0)
Vomiting	10 (16.9)	19 (32.2)	30 (50.8)	0 (0)	0 (0)
Dysuria	48 (81.3)	11 (18.6)	0 (0)	0 (0)	0 (0)
Neutropenia	19 (32.2)	4 (6.8)	28 (47.4)	8 (13.6)	0 (0)
Leukopenia	21 (35.6)	1 (3)	27 (45.8)	8 (13.6)	0 (0)
Anemia	51 (86.4)	6 (10.2)	2 (3.3)	0 (0)	0 (0)
Thrombo-cytopenia	54 (91.5)	2 (3.4)	3 (5.8)	0 (0)	0 (0)
Dermatitis	54 (91.5)	3 (5.0)	2 (3.4)	0 (0)	0 (0)
Abdominal pain	57 (96.6)	1 (1.7)	1 (1.7)	0 (0)	0 (0)
Headache	56 (94.9)	1 (1.7)	2 (3.4)	0 (0)	0 (0)
Constipation	58 (98.3)	1 (1.7)	0 (0)	0 (0)	0 (0)

Treatment Response. Treatment response was evaluated by intention-to-treat. Complete responses were achieved in 49 (83.05%) patients, whereas ten (16.95%) patients had either persistent (5 patients, 8.47%) or progressive (5 patients 8.47%) disease. Among patients with progressive disease, all had systemic progression, and four of these additionally had uncontrolled local disease.

Toxicity. Overall, treatment was very well-tolerated. Toxicity during chemoradiation is shown in Table 3. As expected, the most common toxicities were hematological and gastrointestinal but were mainly grades 1 and 2. Of note, the rate of grade 3 neutropenia and leukopenia was only 13.6% with no grade 4 episodes. So far, two (3.4%) and seven (11%) patients have presented grade 1 and 2 late proctitis.

Survival. At a median follow-up time of 20 months (range, 2-48 months), 16 patients (27.11%) have relapsed: two of these (12.5%) had local and 25 (87.5%) patients systemic relapse. Estimated 30-month overall survival was 63% (Figure 1). The small number of patients precluded any analysis on influence of age and these comorbidities on survival.

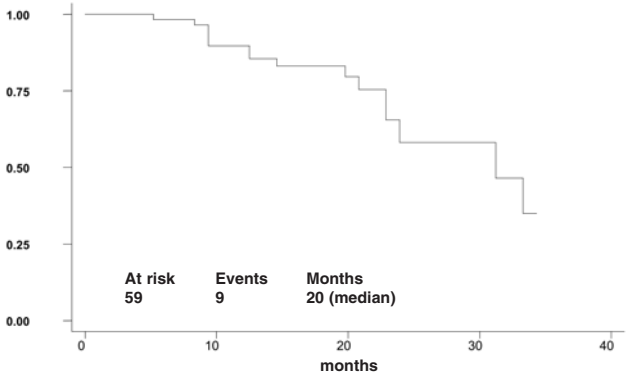

Figure 1. — Overall survival

Discussion

Diabetes mellitus and hypertension are two of the most prevalent chronic diseases which affect populations worldwide. Both conditions damage renal structures through their evolution, despite optimal glycemic and blood pressure control [9, 10]. Likewise, aging is accompanied by decreasing renal function which has a negative impact on the degree of toxicity resulting from chemotherapy, in particular, cisplatin. Thus, older patients demonstrate reduced clearance of total and unbound platinum, with increased severity of cisplatin-induced nephrotoxicity [25-27]. Since in our Institution a substantial proportion of patients with newly diagnosed cervical cancer are older than 70 years and/or have diabetes and hypertension we adopted carboplatin as the radiosensitizer of choice for these patients.

The majority of the studies using carboplatin as a radiosensitizer for the primary treatment of cervical cancer are small phase I or II trials. Despite these limitations, most of these agree on the safety and efficacy of this drug. Micheletti *et al.* reported a complete response rate of 75% in 12 Stage IIB-IIIB patients using a schedule of 12 mg/m^2/day for a total dose of 504 mg/m^2 in 42 days which was equivalent to 250 mg/m^2 every 21 days for two courses [28]. In another study done on IIA-IIIB patients a complete response rate of 86.3% was reported. Fifteen of these 19 patients in complete response were reported alive and disease free at a median follow-up of 15 months [29]. Higgins *et al.* [30] evaluated 31 patients with Stage IBI-IIIB cervical cancer using an initial dose of carboplatin (AUC of 2) which was administered on the first day of radiation therapy and repeated on a weekly basis for six courses. A complete response rate was documented in 28 of 31 patients (90%). Hematological toxicity was observed in less than two percent. After a mean follow-up time of 12 months, 23 patients (74%) remained disease-free. Dubay *et al.* [31] reported the outcomes of 21 Stage IIB-IVA cervical cancer patients who received carboplatin (300 mg/m^2) administered every three weeks at the start of radiation. All patients completed at least three courses of chemotherapy during their radiation therapy. Two patients had grade 3 granulocytopenia, two patients had grade 3 anemia and one patient had grade 3 gastrointestinal toxicity. Thirteen patients (62%) went on to complete all six planned cycles. The average follow-up time was 51.6 months; the pelvic control rate was 76% and overall survival rate was 71%.

In our Institution we have adopted a weekly dose of 133 mg/m^2 based on our dose-finding study where we reported that this dose-level produced 33% of grade 3 leukopenia/neutropenia with no other grade 3 toxicity, except for the skin and lower gastrointestinal tract in less than 20% of patients [21]. This dosing allowed the application of carboplatin for six and five weeks in 78% of patients which is comparable to the number of times cisplatin is administered in a weekly regimen at 40 mg/m^2 [32]. Likewise, chemotherapy did not compromise the dose or time radiation was delivered, and most patients (92%) completed both EBRT and intracavitary therapy.

Chemoradiation with weekly cisplatin or a regimen of cisplatin and 5-fluorouracil at 21-day cycles for locally advanced cervical cancer produces 5-year survival rates between 65% and 83% depending on the proportion of FIGO stages accrued in both protocol [4, 33-35] and non-protocol settings [32]. In this report the expected survival at 30 months follow-up time was 63% which appears slightly lower to that obtained with cisplatin. However, whether this could be the result of the patient population treated or due to the use of cisplatin is not clear. It has previously been reported that comordities and age can have an adverse prognostic influence in cervical cancer patients [36-38]. In contrast, this dose of carboplatin was very well tolerated, with leukopenia and neutropenia below 15% which is remarkable as myelosuppression is the limiting toxicity of this agent.

While the present study suggests that carboplatin is well suited for aged, diabetic and/or hypertensive patients, there are issues that deserve discussion. Although cisplatin has been shown to impair glucose tolerance in rats [39], to induce hyperglycemia [40-42], and to elevate blood pressure in patients [43], these morbidies and age are not contraindications for using cisplatin. In addition, it has been reported that cisplatin is well tolerated in elderly lung cancer patients [44]; and that hyperglycemia, may paradoxically protect the kidney from cisplatin nephrotoxicity in rats [45]. On the contrary, although the literature supports the equivalent efficacy of cisplatin and carboplatin in cervical cancer [11-18], and a recent randomized non-inferiority trial reported no differences in outcome of nasopharyngeal cancer patients receiving either cisplatin or carboplatin concurrent with radiation [46], the apparently slightly lower survival observed in our patients is disturbing, although it could be the result of the small number of patients or the presence of comorbidites. On this basis, we can not recommend the routine use of carboplatin for hypertensive, diabetic or elderly patients. Nevertheless, there is little doubt that carboplatin is better tolerated and to easy administer than cisplatin, therefore a prospective randomized head to head comparison of these agents is merited.

Acknowledgements

Dr. Dueñas-Gonzalez is a recipient of the Cátedra ICP-PUIS UNAM.

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