Out-of-protocol concurrent use of cisplatin and radiation therapy in locally advanced cervical cancer: feasibility and survival

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Summary

Purpose of investigation: We assessed the feasibility, response rates, and overall survival of patients with locally advanced cervical cancer treated with cisplatin-based chemotherapy during radiation therapy on an out-of-protocol basis. *Methods:* Sixty-nine consecutive newly diagnosed untreated patients with locally advanced cervical cancer who received chemoradiation between 1999 and 2003 were retrospectively reviewed. Treatment consisted in external beam radiation followed by one 137-cessium intracavitary application. Cisplatin was administered for six weeks during external beam radiation. *Results:* Treatment was well tolerated, although 52 patients presented some degree of acute adverse toxicity (gastrointestinal 65%, hematological 48%, genitourinary 10%). The 3-year survival rate was 61.8% (95% CI 54.5-69.0), with a mean 41.8 months (95% CI 35.7-48.3). Overall survival after adjusting by FIGO Stage IB_2-IIA and IIB-IVA was 73.9% and 50%, respectively ($p = 0.1839$). Overall survival according to Stages IB_2-IIb and III-IVA was 74.8% and 34.9%, respectively ($p = 0.0376$). *Conclusion:* In patients with locally advanced cervical cancer, adding a weekly regimen of cisplatin to standard pelvic radiation in an out-of-protocol basis is feasible, effective, and showed no unexpected toxicity.

Key words: Locally advanced cervical cancer; Cisplatin; Pelvis radiation therapy.

Introduction

Cytological screening has significantly reduced the rates of cervical cancer in many developed countries. However, cervical cancer remains a leading type of cancer among women, particularly those living in low-income regions of the world [1]. In Spain, due to preventive screening programs, invasive cervical cancer only represents 10.3 cases among 100,000 women/year, with a mortality rate of 3.6 cases among 100,000 women/year. However, up to 25% of these cases are diagnosed in FIGO locally advanced stages [1]. Therefore mortality in these cases rises to 50% compared with the 10% observed in early cervical cancer patients [2].

For many years, the current standard treatment of locally advanced cervical cancer has been exclusively based on radiation therapy. Although chemotherapy has been used in neoadjuvant and in a concomitant modality with radiation therapy to maximize the response to it, until 1999 all studies failed to show a significant advantage of using chemotherapy as a part of the treatment of cervical cancer [3-7]. In 1999 and 2000, five randomized studies using a concurrent chemotherapy schedule showed that the survival rate of patients with cervical cancer treated with radiotherapy alone was lower than with concomitant chemotherapy, and that mortality declined from 50% to 30% [8-12]. Faced with these data, the National Cancer Institute issued a clinical announcement stating, "Based on these results, strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy, with radiation therapy in women who require radiation therapy for treatment of cervical cancer" [13]. Although the search for the ideal "radiation sensitizer" in ongoing, cisplatin chemoradiation therapy is standard treatment for locally advanced cervical cancer [2, 14].

According to the results of the randomized trials supporting the use of cisplatin-based chemoradiotherapy in cervical cancer, we adopted the treatment with cisplatin chemoradiation as routine management of women with locally advanced cervical cancer. The aim of this study was to evaluate feasibility, response rates, and overall survival of patients with locally advanced cervical cancer treated with cisplatin-based chemotherapy during radiation on an out-of-protocol basis.

Methods and Patients

We conducted a retrospective review of 69 consecutive newly diagnosed and previously untreated patients with locally advanced cervical cancer, who received radiotherapy and concurrent cisplatin at the Gynecologic Oncology Unit of the Materno-infantil Vall d'Hebron Hospital in Barcelona, Spain between June 1999 and July 2003. All patients had a histologic diagnosis of cervical carcinoma and were staged according to the FIGO classification using standard pretreatment workup

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studies including magnetic resonance imaging (MRI). Before starting treatment one patient died, five patients were treated in other oncological centers because of breakdown of the lineal accelerator equipment and two more were excluded for concomitant treatment because of renal failure. The baseline characteristics of the patients are shown in Table 1. As this was a retrospective review of patients treated on a routine basis, approval of the institutional review board was not required.

Table 1. — *Patient characteristics*.

Mean follow-up, months (range)	25 (4-63)
Median age, years (range)	56 (24-81)
Menopausal status	63%
Histologic diagnosis, no. (%)	
Squamous cell carcinoma	51 (75)
Adenocarcinoma	11 (16)
Others	6 (9)
FIGO Stage	
IB_2-IIA	37 (54.4)
IIB-IVA	31 (45.5)
Tumor size	
Maximum diameter (range)	5.87 (4–9)
Tumor volume (cm^3) (range)	49.25 (9–191)

A total of 60 patients received external beam radiation using a megavoltage machine (lineal accelerator) with a photon-beam energy of 2.25 MV and isocenter technique to the whole pelvis. Patients were treated with the conventional 4-field box technique. Total dose planned was 45 Gy in 25 fractions (5 weeks, 1.8-2 Gy fractions from Monday to Friday) followed by one 137-cessium intracavitary application within two weeks of finishing external radiation, an isodose of 25 Gy referred to the cervix. The planned total dose to point A was at least 85 Gy. Total treatment duration had to be eight weeks. Treated pelvic volume had to include the whole uterus, paracervical, parametrial and uterosacral regions, as well as the external iliac, hypogastric and obturator lymph nodes. If there was clinical or radiological suspicion of paraaortic lymph node infiltration, we planned an extended field until the T12-L1 vertebral body to include them.

Cisplatin was administered for six weeks during external beam radiation, beginning on the first day of treatment in an outpatient setting. Cisplatin infusion was administered within 2 h before radiation. A dose of 40 mg/m^2 (maximum dose 70 mg) was administered via a peripheral vein to patients in an outpatient setting.

Response to treatment was evaluated clinically, colpocytologically, and histologically when necessary at three months after the end of treatment. Response was also evaluated radiologically by MRI at three and six months. Complete response was defined as no clinical or cytological evidence of disease. Partial response was defined if there where a decrease > 50% in initial lesion size and no new lesions. Persistent disease was considered with any less-than-50% response. Finally, progression was defined if there was an increase > 25% in initial lesion size or new lesions appeared [15].

Upon treatment completion and response evaluation, patients were evaluated every three months for the first two years and every six months thereafter until five years of follow-up were completed. At each control, a physical, pelvic and colpocytological examination, blood counts and clinical chemistry were performed. Annually chest X-rays and MRI were conducted. If persistent or recurrent disease was suspected, it was confirmed by biopsy whenever possible.

Acute and chronic toxicity to chemoradiation were evaluated according to EORTC/RTOG common toxicity criteria [16]. The acute side-effects were defined as those occurring during or within 90 days of completing radiotherapy. During treatment, blood counts and chemistry profiles were performed prior to each cisplatin administration. Late reactions were defined as those occurring 90 days or more from completing radiotherapy.

Statistical analysis

Overall and progression-free survival times were analyzed and registered from date of diagnosis to date of death or date at last visit, and from date of diagnosis to date of progression or relapse, respectively. Curves were constructed using the Kaplan-Meier method [17]. Due to the low number of patients, they were grouped depending on FIGO stage. We named bulky stages: IB_2-IIA and locally advanced Stages: IIB-IVA. Univariate and multivariate analyses were carried out to examine the relationship between the most frequent variables considered in the literature as prognostic factors for treatment response and occurrence of response or not [18-25]. The SPSS (Windows version 11.0) statistical program (SPSS, Inc., Chicago) was used for the analysis of data.

Results

A total of 60 patients who received chemoradiation were analyzed. The mean age was 56 years (range 24-81 years). A total of 25% of cases were adenocarcinomas, and the distribution according to FIGO Stage was IB2-II_a: 54.4% and IIb-IV_a: 45.5%. The mean tumor diameter at diagnosis was 5.87 cm (range 4-9 cm).

Table 2 shows treatment data. Overall treatment time was eight weeks (range 6-11.7 weeks). The mean dose of external beam radiation was 45 Gy (26-65 Gy). Overall 68.3% of patients completed external beam and intracavitary therapy. Nineteen patients (31.7%) did no receive brachytherapy because of anatomic problems that conditioned technical difficulties for insertions (n = 11), progression (n = 2), fistula (n = 2), no indication (n = 3), and discontinuation of treatment after external beam (n = 1). With regard to chemotherapy, the majority of patients (71.7%) received the six planned cycles; furthermore 91.8% of patients received at least four cycles.

Table 2. — *Treatment data*.

Interval between diagnosis and treatment, weeks (range)	7 (2.7-16.8)
Median external radiation duration, weeks (range)	6 (2-24)
Median total treatment duration, weeks (range)	9.8 (9.1-11.2)
Mean dose of external radiotherapy (range)	45 (26-65)
CDDP mean cycles	5 (1-7)
Intracavitary radiation	
N (%)	41 (68.3)
Mean (SD) dose (Gy)	26 (15-35)

Overall, treatment was well tolerated, although 52 patients (83%) presented some degree of acute adverse toxicity. The most common acute adverse effects were gastrointestinal (n = 39, 65%), hematological (n = 29; 48%), and genitourinary (n = 6, 10%). The most frequent hematological toxicity was anemia (n = 10; 10%). The

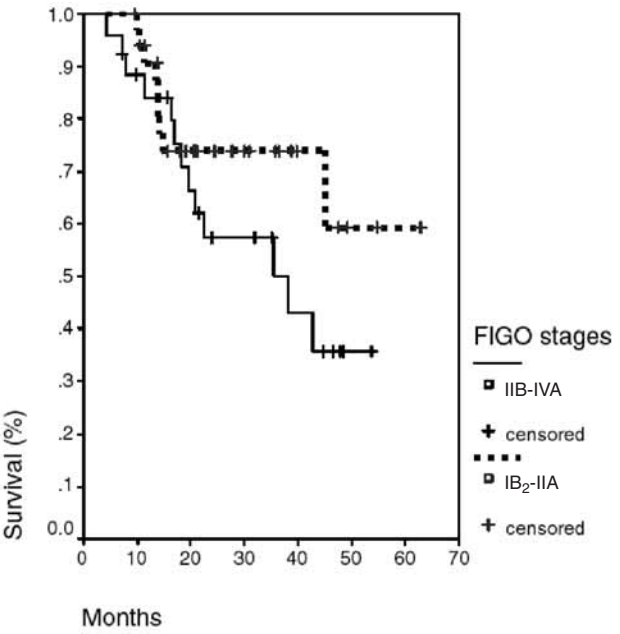

Figure 1. — Overall survival after adjusting by FIGO stage.

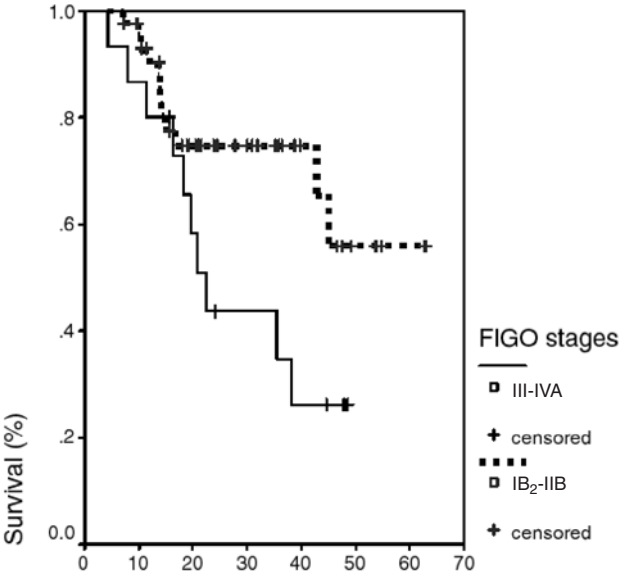

Figure 2. — Overall survival after grouping IIb with bulky stages (IB2-IIa).

most common acute grade 4 toxicity was gastrointestinal (n = 2) with peritonitis and perforation of the sigmoid colon that obliged putting off the treatment until patients recovered. A total of 26.7% of patients referred some gastrointestinal toxicity (G1-2) after 90 days of follow-up. Only one patient presented a fatal late complication occurring six months after the first day of radiotherapy because of an intestinal occlusion secondary to enteritis.

Treatment response was evaluated by intention-to-treat basis. After finishing chemoradiation therapy, complete response was achieved in only 16 patients (26.7%), partial responses in 30 cases (50%), whereas 13 patients had either persistent (n = 11) or progressive (n = 3) disease. Among patients who received brachytherapy (n = 41), overall complete response was achieved in 85.4% of patients. Therefore, 91.7% of partial responses became complete after intracavitary therapy.

At a median follow-up time of 25.4 months (range 4-62 months), 38 patients (63.3%) were alive, 35 with no evidence of disease. According to FIGO stage, 73% of these patients were FIGO IB_2-IIA, and 50% FIGO IIB-IVA. Overall survival at three years was 61.78% (95% CI 54.5-69.0), with a mean of 41.8 months (95% CI 35.3-48.3). Overall, survival after adjusting by FIGO stage was 73.9% and 50.05%, respectively (Figure 1). However, differences were not statistically significant (long rank, p = 0.1839). Overall survival according to Stages IB_2-IIB and III-IVA significantly changed to 74.8% (95% CI 67.9-81.7) and 34.9% (95% CI 21.7-48.1), respectively (p = 0.0376) (Figure 2).

Prognostic factors for treatment response identified after carrying out the univariate analysis were tumor volume lower than 50 cm^3, tumor diameter < 6 cm, non-suspicious lymph nodes in MRI and intracavitary radiation ($p < 0.05$) (Table 3). After performing the multivariate analysis only the application of endocavitary radiation was identified as an independent prognostic factor to treatment response. No association was found between treatment response and increasing FIGO stage, age, prolonged overall treatment time or waiting time to start treatment.

Table 3. — *Prognostic factors for treatment response. Univariate analysis.*

	Treatment Response	
	Odds ratio	95% CI
Intracavitary radiation	11.375	2.079-62.232
Tumor diameter ≤ 6 cm	6.643	1.189-37.107
Tumor volume ≤ 50 cm^3	6.458	1.100-37.918
Non suspicious lymph nodes (MRI)	6.417	1.204-34.193

Table 4. — *Comparison of overall survival of large randomized trials.*

Study	Reference	FIGO stage	Treatment	Survival at 3 years	RR Control group
RTOG	Morris	IB2-IV_a ±	CDDP + 5FU	75	0.52
9001	[11]	Pelvic LN +	–	63	–
GOG 85	Whitney	IIb-IV_a	CDDP + 5FU	67	0.72
	[8]		H-Urea	57	–
GOG 120	Rose	IIb-IV_a	CDDP	65	0.58
	[9]		CDDP+5FU+ H-U	65	0.61
			H-Urea	47	–
NCIC	Pearcey	Ib > 5 cm	CDDP	69	0.9
	[32]	IVa	–	66	–
Vall d'Hebrón	Mancebo	Ib2-IV_a	CDDP	61	–
Vall	Mancebo	Ib2-II_a	CDDP	74	Reference
d'Hebrón		IIb-IV_a	CDDP	50	1.9

Discussion

Until recently, the greatest strides in reducing cervical cancer mortality have occurred with the advent and implementation of screening programs. However, locally advanced cervical cancer remains a significant health problem. Prognosis of patients with locally advanced cervical cancer has remained unalterable during 20-30 years, when therapeutic options were basically surgery or radiation therapy. However, great advances have also been made in the treatment of locally advanced cervical cancer after the results of several important clinical trials [8-12]. A subsequent meta-analysis of 19 randomized controlled trials with a total of 4,580 patients confirmed that the addition of chemotherapy to radiation therapy improved progression-free and overall-survival of these patients [26-28], which represents an 11-12% absolute benefit in survival.

Notwithstanding these results, there are not a lot of data about feasibility and results of concurrent chemotherapy and radiotherapy in the routine management of locally advanced cervical cancer in an outside research setting [29-31]. However, considering differences in the chemotherapeutic regimens and patients included, our data show comparable overall survival to chemoradiotherapy arms of large randomized trials and others (Table 4). We found a 36.6% mortality that is near the 45% at five years reported by Whitney *et al*. [8]. A total of 61.7% of our patients had a median survival of 45 months, similar to that in the NCIC study [32]. It should be noted that 50% of our patients with FIGO Stages III-IVA survived three years compared with 65-67% of survival reported by Rose and Whitney [8, 9]. Although it has been reported that distant metastasis to lymph nodes is one of the most important prognostic factors of survival in locally advanced cervical cancer, we did not exclude women with proven or suspicious spread to the paraaortic lymph nodes. This could be the main reason for survival differences with data reported by these authors.

We did not conduct a randomized comparison to radiotherapy-only because of ethical implications; however, a comparison could be made to previous results published by Denton *et al*. [33] in an English national audit of the management and outcome of carcinoma of the cervix treated with radiotherapy in 1993. This group showed overall survival at five years of 47% (Stages Ib [62%], IIb [47%], IIIb [23%]). A more recent single-center audit by Taylor and Powell [34] identified 69 women with cervical carcinoma treated with radical chemoradiation. After medial follow-up of 15 months they found a 40% relapses. It is important to mention that doses administered were lower than those in US randomized trials or in our study.

Overall, 68.3% of patients completed external beam and intracavitary therapy. This is lower than Addenbrooke *et al's* experience [35]. They reported that successful brachytherapy was possible in 84.7% of women. In our study like others [36-39], successful brachytherapy was the only independent prognostic factor associated with response to treatment. Thus, it is important to remark that efforts should be made to improve successful brachytherapy rates in order to improve overall response and overall survival.

It should be emphasized that when we included patients with FIGO Stage IIB, overall survival in this group did not change significantly; these results are similar to those reported by Morris *et al*. [11]. This finding has important prognostic implications that should be deeply explored in order to offer most accurate information to patients.

Acute toxicity of chemoradiation for LAC has been reported in several phase II and III studies [8, 9, 11, 31, 40]. A comparison of the results is difficult because of the differences in the chemotherapeutic regimens, the radiotherapy delivered and whether or not surgery was performed. In general, as in our study, the main toxicity encountered during combined chemoradiation is hematological or gastrointestinal, which is well tolerated and rarely obliges putting off treatment.

In conclusion, in patients with locally advanced cervical cancer, adding a weekly regimen of cisplatin to standard pelvic radiation in an out-of-protocol basis is feasible, effective, and showed no unexpected toxicity.

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