Response to neoadjuvant chemotherapy with paclitaxel and cisplatin in locally advanced cervical cancer

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Summary

Purpose: The purpose of this study was to evaluate the efficacy and toxicity of paclitaxel and cisplatin as neoadjuvant chemotherapy for patients with Stage IB2 to IIB cervical cancer and determine factors accountable for response. *Materials and Methods:* From November 2009 to January 2011, a total of 19 patients with Stage IB2 to IIB cervical cancer were treated with three ten-day courses of paclitaxel 60 mg/m^2 and cisplatin 80 mg/m^2 followed by type III radical hysterectomy and adjuvant therapy if indicated, or chemoradiation in non-resectable patients. *Results.* Clinical response occurred in 79% (15/19) of patients, including 10.5% (2/19) with complete response, and 68.5% (13/19) with partial response. Four (21%) patients were nonresponders including 16% (3/19) with stable and 5.2% (1/19) with progressive disease. Resectability rate was 68.5% (13/19). Pathological optimal response rate was 46% (6/13) including, 15% (2/13) with complete and 31% (4/13) with residual disease < three mm stromal invasion response (PR1). Suboptimal response (PR2) (residual disease with > three mm stromal invasion) was 54% (7/13). It appears that both clinical and pathological response were correlated with tumor stage and size. Clinical response was seen in 87.5% of tumors sized = < eight cm vs 33.3% of tumors sized > eight cm ($p = 0.166$) and optimal pathological response was seen in 66.7% of tumors sized < four cm vs 28.6% of tumors sized four to eight cm, ($p = 0.286$), although because of small number of patients, the difference was not statistically significant. Adjuvant therapy was necessary for 38.5% (5/13) patients. Toxicities were not life-threatening and all manageable. *Conclusions*: The present results suggest that neoadjuvant chemotherapy (NAC) with paclitaxel and cispaltin is a highly active and well-tolerated regimen. Best candidates are patients with stages IB2/IIA bulky and IIB non-bulky than IIB bulky groups.

Key words: Cervical cancer, Neoadjuvant chemotherapy; Cisplatin; Paclitaxel; Pathological response.

Introduction

Worldwide, cervical cancer is the second most common malignancy [1] and is the most prevalent female malignancy in many developing countries. Eighty percent of the world's new cervical cancer cases and resulting deaths occur in developing countries, where 80% of cases are diagnosed with locally advanced disease. There is no agreement on the best approach for bulky (≥ four cm in diameter of tumor) or locally advanced cervical cancer (LACC), whose prognosis remains poor in spite of the therapeutic advances achieved in recent years. For many, chemoradiation is now considered the treatment of choice for these patients, but a substantial proportion of patients treated with chemoradiation will have persistent or progressive disease after primary treatment. Thus different therapeutic approaches such as neoadjuvant chemotherapy (NAC) were introduced.

Tierney *et al.* [2] in a meta-analysis study based on individual participant data (IPD) compared NAC followed by surgery with radical radiotherapy and showed a highly significant benefit of NAC with an absolute improvement of 14% in five-year survival from 50% to 64%. However nowadays NAC has not been adopted as the standard of care and is still considered investigational. Several explanations for this hesitancy can be given, which probably the most important is that this treatment modality being compared to radiotherapy alone, which is inferior to today's standard of care of chemoradiation.

There are two ongoing randomized trials, the EORTC 55994 and Tata Memorial trial, comparing chemoradiation with chemotherapy before surgery. An important topic is to assess which chemotherapy scheme is more effective. The meta-analysis results suggest that it seems to be prudent to use a short cycle length and dose intense NAC scheme [2]. In addition several trials have shown that patients achieving pathological complete response to NAC do experience a significant improvement in rates of overall survival [3, 4].

The studies using regimens based on cisplatin and drugs such as bleomycin and vincristine have shown that these agents are clearly not the most effective agents against cervical cancer [5, 6]. With these regimens the overall response rate varied between 47% and 88%. However with newer drug regimens such as cisplatin plus gemcitabine [7], taxanes [8], ironotecan [9], vinorelbine [10], oxaliplatin [11], ifosfamide [8], overall response rates were achieved in the range between 78%-95% and pathological complete response were 14%-35.7%. In the present study the authors used the combination of cisplatin and paclitaxel.

The aim of this study was to focus on the efficacy (clinical and pathological results) and tolerability of induction chemotherapy followed by radical resection in patients with Stages IB2 to IIB cervical cancer, and to determine the prognostic factors responsible for clinical and pathological response.

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Materials and Methods

From November 2009 to January 2011, 19 untreated patients with Stage IB2 through IIB cervical cancer who were hospitalized at Valiasr Hospital were eligible for the study. Further entry criteria were age < 75 years, performance status (PS) of ≤ 2 according to the WHO criteria, adequate bone marrow, renal and hepatic functions, as determined by a Hb ≥ 9 gr/dl, WBC > 3,000/mm^3, and platelet count of at least 100,000/mm^3, total bilirubin and transaminase and creatinine less than the 1.5 times the upper limit of normal, a normal posteroanterior CXR, signed written informed consent.

Exclusion criteria included: severe systemic or uncontrolled disease that precluded the use of chemotherapy, preexisting neuropathy of any cause, pregnancy or lactation, mental illness, previous or concomitant malignancies except non-melanoma skin cancer, previous radiotherapy or chemotherapy.

All patients were staged based on FIGO clinical staging criteria for cervical cancer. Tumor size was measured before the NAC by pelvic examination and magnetic resonance imaging (MRI). Following parameters were obtained from imaging studies: tumor size, parametrial invasion, lymph node metastasis, and vaginal involvement. The NAC regimen consisted of paclitaxel (60 mg/m^2) and cisplatin (80 mg/m^2). NAC was administered on day one every ten days.

Three consecutive cycles were planned. Complete blood count and platelet count plus routine 12-channel biochemistry were performed before each cycle. The toxicity of the regimen was determined according to the WHO toxicity criteria by grade. Response to NAC was determined ten days after the third cycle of chemotherapy by pelvic examination and MRI. Clinical response was evaluated according to the WHO criteria as follows: complete response: the disappearance of all measurable disease; partial response: a 50% or more reduction of the product of two perpendicular tumor diameters; stable disease: less than 50% reduction; progressive disease: greater than 25% increase in tumor.

After NAC, if the multidisciplinary team judged that the disease could be resected obtaining margins free of disease, patients were submitted to type III radical hysterectomy and bilateral pelvic lymphadenectomy (patients with clinical objective response). The surgery was performed within two or three weeks after completion of the third cycle. Those patients who were judged to have a non-resectable disease (patients with stable or progressive disease) underwent standard chemoradiation.

For the surgically treated patients, the authors also evaluated the pathologic response. Pathologic responses were defined as follows: Optimal pathologic response (OR) included a complete disappearance of tumor in the cervix with negative nodes (CR) or a residual disease with < three mm stromal invasion including insitu carcinoma (PR1). Suboptimal response consisted of persistent residual disease with > three mm stromal invasion on surgical specimen (PR2).

Postoperative concurrent chemoradiation was administered to high-risk patients who were defined as those with at least one major risk factor among: positive nodes, parametrial involvement, and positive surgical margins or two or more intermediate risk factors among: tumor size, depth of invasion (> 1/3 cervical stromal invasion) and lymph-vascular space invasion (LVSI). All patients had a follow up visit every three months until the end of the second year and then every six months until the last follow up.

Statistical methods: data was descript as median (range) for continues and frequency (percentage) for categorical variables. The Fisher's exact test was used to assess the association between clinical or pathological response rates and baseline tumor characteristics.

Table 1. — *Tumor characteristics at baseline.*

	No.	%
FIGO Stage:		
IB2	1	5.3
IIA bulky	1	5.3
IIB non-bulky	7	36.8
IIB bulky	10	52.6
Histologic type:		
SCC	17	89.4
Adenocarcinoma	1	5.3
Adenosquamous	1	5.3
Tumor size:		
< 4 cm	7	36.8
4 - 8 cm	9	47.4
> 8 cm	3	15.8

SCC: squamous cell carcinoma.

Table 2. — *Chemotherapeutic response according to clinicopathologic parameters.*

Measured parameters	No. of patients	Clinical response				Patients with clinical response		*p*
		CR	PR	SD	PD	No.	% (RR)	
Age group (years)								0.303
= < 50	9	0	6	3	0	6	66.7	
> 50	10	2	7	0	1	9	90.0	
Stage								0.756
IB2/IIA bulky	2	0	2	0	0	2	100	
IIB non bulky	7	2	4	1	0	6	85.7	
IIB bulky	10	0	7	2	1	7	70.0	
Tumor size								0.166
< 4 cm	7	2	4	1	0	6	85.7	
4 - 8 cm	9	0	8	1	0	8	88.9	
> 8 cm	3	0	1	1	1	1	33.3	

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, RR: response rate.

Results

A total of 19 patients were enrolled in this prospective study of NAC before surgery. The tumor characteristics are shown in Table 1. The median patient age was 52 years (range 30-72).

Clinical response to NAC

Clinical response occurred in 79% (15/19) of patients, including 10.5% (2/19) with complete, and 68.5% (13/19) with partial response. Sixteen percent (3/19) of patients showed stable and 5.2% (1/19) had progressive disease. Thus 15 (79%) patients were NAC responders and four (21%) were non-responders. The correlation between response rate and clinicopathological parameters has been detailed in Table 2. Whereas 90% of patients aged more than 50 years responded clinically to NAC, this rate was 66.7% in ages = < 50 years old.

This result may be affected by the difference in tumor stage and size between the age groups, because when patient age group was cross-tabulated by stage and tumor size, two age groups were significantly different according to stage of tumor ($p = 0.049$) and were considerable different according to size of tumor. Both patients (100%) with Stage IB2 and

Table 3. — *Pathological data of 13 patients submitted to surgery.*

	No. of patients	%
Parametrial involvement		
Yes	0	
No	13	100%
LN metastases		
Yes	1	7.6%
No	12	92.3%
Positive surgical margin		
Yes	0	
No	13	100%
Vaginal involvement		
Yes	1	7.7%
No	12	92.3%
LVSI		
Yes	2	15.4%
No	11	84.6%
Cervical stromal invasion		
> 1/3	5	38.5%
< 1/3	8	61.5%
Residual lesion size		
No tumor	2	15.4%
< 0.6 mm	5	38.5%
0.6 mm-2 cm	3	23.0%
> 2 cm	3	23.0%

LVSI: lymph-vascular space invasion.

Table 4. — *Histologic response to initial chemotherapy by characteristics of patients.*

Parameters	No. of patients	Pathological response CR	PRI	PR2	Optimal response No. (%)	*p*
Age group (years)						0.559
= < 50	4	1	0	3	1 (25.0)	
> 50	9	1	4	4	5 (55.6)	
Stage					0.476	
IB2/IIA bulky	2	1	1	0	2 (100)	
IIB non bulky	6	1	3	2	4 (66.7)	
IIB bulky	5	0	1	4	1 (20.0)	
Tumor size						0.286
< 4 cm	6	1	3	2	4 (66.7)	
4 - 8 cm	7	1	1	5	2 (28.6)	

CR: complete response, PR: partial response.

Table 5. — *Toxicities according to WHO criteria expressed as n (%) of patients.*

Toxicity	Grade 1	2	3	4
Anemia	4 (21)			
Nausea/vomiting		6 (32)	3 (16)	1 (5)
↑Creatinine	2 (10)			
Skin allergy		1 (5)		
Hair loss		3 (16)	2 (10)	3 (16)
Cardiac		1 (5)		
Neuropathy			1 (5)	
Pain		1 (5)		

IIA bulky disease had clinical response. Whereas the clinical response decrease to 85.7% in Stage IIB non-bulky and 70% in Stage IIB bulky disease. Clinical response was considerable lower in tumors sized > eight cm (33.3%) than tumor sizes of four to eight cm (88.9%) or < four cm (85.7%), (p = 0.166), although because of small number of patients, the difference is not statistically significant.

Local therapy

Two of the 15 patients considered surgically resectable refused surgery and underwent chemoradiation in other centers. Thus surgery was performed on 13 patients. Resectability rate was 68.5% (13/19). The four patients with SD and PD were unresectable (21%) and were subsequently referred for chemoradiation. Type III radical hysterectomy with lymphadenectomy was performed in 12 patients and in one patient a protocol violation occurred during surgery and simple hysterectomy with lymphadenectomy was performed. In this patient tumor necrosis in the cervix was too extensive that the cervix was separated off the uterus during surgery, so radical hysterectomy was technically impossible.

Pathological responses

The analysis of the surgical specimens showed complete pathological response in 15% (2/13), and PR1 response in 31% (4/13) of patients (46% optimal response rate) and suboptimal response (PR2) in 54% (7/13) of patients. Pathological data is shown in Table 3. All patients had free surgical margins. No patient had parametrial involvement. Lymph node metastases were present in one patient (7.5%), although MRI findings before chemotherapy showed lymph node involvement in six patients.

In six patients with parametrial invasion reported by MRI, after completion of chemotherapy, no parametrial invasion was observed pathologically. Thus the findings show that there was no correlation between clinical and pathological findings in this study. Table 4 shows the pathological response according to patient's characteristics.

Although due to the small numbers of cases, the authors cannot show any statistically significant association between pathological response and baseline characteristics, but found that optimal response rate was considerably lower in age group < 50 than = > 50 (25% vs 55.6%), Stage IIB bulky than IIB non-bulky (20% vs 66.7%) or than IB2/IIA bulky (20% vs 100%) group, and tumor size four to eight cm than < four cm (28.6% versus 66.7%). Here the cut-off point for pathological response was four cm.

According to histological findings and evaluation of prognostic factors, postoperative adjuvant therapy was recommended for (7/13) 54% of patients although it was necessary for (5/13) 38.5% of patients, because in one patient, only simple hysterectomy was performed, and in the other despite having PR1 response, adjuvant chemotherapy was used due to recommending it in some other studies [12].

Table 5 summarizes the compliance and toxicities encountered during the treatment of NAC. Hematologic toxicity was anemia of grade 1-2 which occurred in four (21%) patients, there was no grade 3 or 4 toxicity. Non hematological toxicity consisted of nausea/vomiting and alopecia. Grade 1-2 nausea/vomiting occurred in six (31.5%) patients and grade 3-4 in four (21%) patients. Grade 1-2 alopecia occurred in three (16%) patients and grade 3-4 occurred in four (21%) patients.

Discussion

NAC represents a promising alternative to surgery or radiotherapy as the initial treatment of LACC. Response to chemotherapy has been confirmed as a potent predictor of survival. In the study by Benedetti-Panici *et al.* on 130 patients, Stage IB2-III cervical cancer treated with NAC containing cisplatin, bleomycin ± methotrexate, followed by surgery, the correlation above is supported by the fact that the parameters significantly associated with survival were the same factors as those predicting response to chemotherapy. [13]

In the present study, clinical objective response was observed in 79% (15/19) of patients. Overall response rate in the present study is comparable with response rate of 78%-95% observed in published phase II trials that used newer drug regimens as NAC [7-11].

Identifying the factors predicting chemoresponsiveness may therefore allow for a more rationale selection of patients. In the long-term follow up study by Benedetti-Panici *et al.* on 130 patients as mentioned above, factors predicting of response were FIGO Stage (IB2-IIB vs III), histotype (SCC vs adenocarcinoma), cervical tumor size (four to five cm vs > five cm), the extension of parametrial involvement clinically (absent-monolateral vs complete bilateral) [13]. In the study by Sardi *et al.*, the most powerful predictor of response was pretreatment tumor volume. The critical pretreatment tumor volume was 84 cm^3 (4.85 cm) in diameter [14]. In the study by Chen *et al.,* the two parameters responsible for response, were tumor size and histologic type. In this study, tumors larger than eight cm had significantly poorer response than those with smaller size. The response was still 63.2% in tumors with a diameter of six to eight cm and it decreased to as low as 41.7% in tumors larger than eight cm [15].

The present study was not powered enough to statistically detect the predicting factors of clinical and pathological response, due to small number of patients. Nonetheless the authors found that some of baseline measured parameters may be a considerable predicting factor. These clinically important factors were tumor stage and size. The cut-off point for the tumor size in this study was eight cm, which is in accordance to Chen *et al.* study [15]. The present authors noted that response rate was still 89% in tumors with a diameter of four to eight cm and it decreased to 33% in tumors larger than eight cm, which suggests that extra large tumors may be poor candidates for NAC. The studies on NAC prior to surgery, underscore the importance of achieving pathological response as a potent prognostic factor for survival. The meaning of pathological response remains unsettled.

In the SNAPO1 Italian collaborative study performed by Buda *et al.*, achievement of optimal pathological response (OR) was a strong independent predictor of survival (HR = 5.88, $p < 0.0001$). The importance of OR was as much that, it was stated that OR may be a surrogate endpoint for survival [4]. In the study by Candelaria *et al.*, the criteria for response were further more strict than the SNAPO1 study. In this study, complete pathological response, but no near-complete or partial response was associated with longer survival [3].

The combination of cisplatin and paclitaxel in the present study induced an optimal response rate of 46% (6/13) including complete pathological response rate of 15% (2/13) and PR1 response of 31% (4/13). These results approximate the results of the studies incorporating newer drug regimens in the NAC settings. In the study by Park *et al.* with the same regimen as the present, on 43 patients, complete pathological response was 11.6% [16] and the long- term follow up of that study showed a five-year survival rate of 89.2% among the 37 patients followed up [17]. Thus the high rate of pathological complete response in the present study may be translated to a high survival rate as the Park study.

A primary objective of chemotherapy is to increase operability rate. In fact, undergoing surgery after chemotherapy represents one of the most important prognostic factors [18]. However response to chemotherapy is not the sole factor determining operability, the aggressiveness of the surgical team also plays an essential role and it requires a highly motivated team of surgeons to attempt surgical resection in cases with no optimal response to chemotherapy. This was shown in Dueñas-Gonzalez *et al.* studies in which, in their primary trials using gemcitabine + cisplatin [7] and oxaliplatin + gemcitabine [11] the operability rate was 60% and 70% respectively and in their further protocol for comparable cases using carboplatin + paclitaxel, the resection rate was 95% [19]. They stated that this high rate was due to the fact that operability was defined intraoperatively.

In the present study, the resectability rate was 68.5% (13/19) which is comparable with other studies with high rate of resectability. The status of lymph nodes is the most important prognostic factor in cervical cancer. In the ten-yr follow up study by Hwang *et al.* on 80 patients with Stage IB2-IIB cervical cancer treated with VBP followed by radical hysterectomy, the only significant risk factor for recurrence was pelvic lymph node involvement ($p = 0.0016$) [20]. In the present study, positive lymph nodes were seen only in one patient (7.5%).

Several studies have reported a pelvic lymph node metastases rate of seven to 25% after NAC for stages IB-IIB patients [21, 22]. The present results are in the range of the least rates. The better results in this study may be due to the efficacy of cisplatin + paclitaxel combination, or the selection of appropriate stages in the study (IB2-IIB). It is worthwhile to note that in this study, no patients had parametrial involvement or positive surgical margins despite seven of these impressed clinically with parametrial involvement and six of these reported by MRI post chemotherapy. This lack of correspondence between clinical and pathological parametrial infiltration has already been observed in other studies [23, 24], and it shows that the clinical suspicion of parametrial disease should not necessarily contraindicate a radical hysterectomy.

In the present study, adjuvant therapy based on pathological risk factors was necessary for 54% (7/13) of patients. The percentage of patients who received adjuvant therapy was comparable with other studies that used same guidelines for adjuvant therapy. In the study by Lee *et al.*, comparing 31 patients with Stage IB2-IIA bulky cervical cancer in the NAC followed by radical hysterectomy and 41 patients in the radical hysterectomy group, due to decreasing risk factors, adjuvant therapy was performed on 51.6% for NAC group compared to 82.9% in the primary R.H group ($p = 0.005$) [25].

Cisplatin and paclitaxel were well-tolerated. The most common hematologic toxicity was anemia which was mild. The most common non-hematological toxicity was reversible alopecia and nausea and vomiting which never caused treatment interruption and no patient required dose reduction. The limitations of this study were the small number of patients and limited long-term follow up. However the follow up of the patients in this study will be continued and the results will be reported in the future.

These preliminary findings indicate that NAC with paclitaxel and cisplatin is highly active and well-tolerated for patients with Stage IB2 to IIB cervical cancer, making surgery possible for patients with tumors considered inoperable and improve pathologic prognostic factors, and thereby decreasing the need for adjuvant therapy. Best candidates are patients with Stages IB2/IIA bulky and IIB non-bulky groups. A randomized phase III trial is required to establish the value of NAC/surgery with or without adjuvant chemoradiation vs standard chemoradiation.

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