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Neoadjuvant Chemotherapy Followed by Radical Surgery in Treatment of Locally Advanced Cervical Carcinoma

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Abstract

Background & Objective: Cervical cancer is the second cause of cancer death in women with about 70% of patients identified at an advanced stage. Currently, platinum based concurrent chemo radiotherapy is the standard of care for locally advanced cervical carcinoma., poor prognosis and survival were reported in patients with tumors larger than 4 cm in diameter, to improve these results, a new treatment modality with Neoadjuvant Chemotherapy (NAC) followed by radical surgery or chemoradiotherapy has been evolved. This study was conducted to assess the efficacy of neoadjuvant chemotherapy in down staging and achieving operability in locally advanced cervical carcinoma.

Patients & Methods: Thirty seven female patients with pathologically proven locally advanced cervical carcinoma stage (IIB up to IIIB) were included into this prospective study. All patients received neoadjuvant chemotherapy consisted ofcisplatin 75 mg/m^2 (or carboplatin AUC 5) and paclitaxel 175 mg/m^2 on day 1 for a maximum of 3 cycles. Assessment of operability was done 2 weeks after the third cycle by MRI and examination under anesthesia. Surgically candidate patients were referred for radical hysterectomy.

Results: Among the 37 patients treated with neoadjuvant chemotherapy, 29 patients (78.4%) achieved response (CR+PR). Complete response was detected in 7 (18.9%) patients, 22 (59.5%) patients expressed partial response, 8 (21.6%) patients had stable disease; no progressive disease was detected in any of the patients, of the 29 patients who achieved response, 20 (69%) patients (54.1% of the total 37 patients) became resectable & underwent surgery.

Conclusion: In conclusion, neoadjuvant chemotherapy is an efficient and tolerable treatment option in down staging of locally advanced cervical cancer also, it represents plus radical surgery a preliminary local control for locally advanced stages, especially if access to radiation oncology centers is limited with long waiting lists.

Keywords: Cervical carcinoma; Neoadjuvant chemotherapy; Cisplatin; Paclitaxel; Radical surgery

Introduction

Cervical cancer represents the second commonest cancer in women worldwide, with 500,000 new cases and 300,000 deaths reported yearly [1].

About 70% of cases are identified at an advanced stage [2]. According to the International Federation of Gynecology and Obstetrics (FIGO) staging system, a locally advanced cervical cancer includes stage IB2 to IIIB [3].

The best treatment for stages IB2, IIA2, and IIB cervical cancer still in conclusive. Treatment modalities include radical surgery plus or minus adjuvant RT, Neoadjuvant Chemotherapy (NAC) plus radical hysterectomy with or without adjuvant RT, and concomitant chemo radiation [4].

Currently, platinum based concurrent chemoradiotherapy is the gold standard for locally advanced cervical carcinoma [5].

Unfortunately, poor prognosis and survival were reported in patients with masses larger than 4 cm in diameter. To improve these findings, a new treatment modality with Neoadjuvant Chemotherapy (NAC) followed by radical surgery or chemoradiotherapy has been evolved [6].

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Table 1: Patients characteristics.

Characteristics	No (%)
Age (years)	
Median	50
Range	(37-70)
ECOG performance status	
0	27 (73%)
1	8 (21.6%)
2	2 (5.4%)
FIGO staging	
IIb	22 (59.5%)
IIIa	3 (8.1%)
IIIb	12 (32.4%)
LN status	
N0	27 (72.9 %)
N1	10 (27.1%)
Tumor size (cm)	
Median	6
range	(4-9.5)

SCC: Squamous Cell Carcinoma

Table 2: Tumor response.

Response	No	%
Complete response (CR)	7	18.9
Partial response(PR)	22	59.5
Stable disease(SD)	8	21.6
Progressive disease(PD)	0	0

In Europe, Japan and Latin countries, NAC followed by surgery has been considered as an alternative treatment option, several pilot studies have proved efficacy of neoadjuvant chemotherapy plus surgery over RT alone as regard Overall Survival (OS) and Disease-Free Survival (DFS) [7].

More recently, neoadjuvant chemotherapy plus radical surgery has gained wider acceptance as an alternative treatment modality [8-10].

Neoadjuvant chemotherapy has many advantages: decreasing tumor size making surgery easier with improved rate of complete resection, decreased pelvic recurrence rate significantly, decreasing rate of parametrial invasion and lymph node metastasis, better brachytherapy distribution, minimal radiation toxicity, and 15% absolute increase of 5-year survival [4,11].

Cisplatinis the most effective drug used in NAC regimens for treatment of cervical carcinoma [5].

This trial was conducted to evaluate the efficacy of neoadjuvant chemotherapy in down staging and achieving operability in locally advanced cervical carcinoma. The primary endpoints were response to chemotherapy and resectability achievement, while the secondary was treatment toxicity.

Patients and Methods

After acceptance of Mansoura Faculty of Medicine Institutional Research Board (MFM IRB, code R.18.04.158), this prospective study was conducted in the department of clinical oncology & nuclear medicine in collaboration with the department of surgical oncology, Oncology Center, Mansoura University, from January 2016 to January 2018.

Thirty seven female patients with pathologically proven locally advanced cervical carcinoma stage (IIB up to IIIB) were included into this prospective study. The patient performance status was ≤ to 2, according to Eastern Cooperative Oncology Group (ECOG) score. Patients enrolled should be chemotherapy naïve with no history of cancer diagnosis.

Patients with metastatic cervical cancer, systemic illness (cardiac, respiratory, and hepatorenal), preexisting neuropathy, and those who had prior chemotherapy or radiotherapy were excluded.

All participants have signed an informed consent before enrollment into the study.

Before entering the study, general, abdominal, vaginal, and rectal examinations were done. Laboratory tests, cystoscopy, proctoscopy, CT scan of the chest, abdominopelvis and or MRI were done. Clinical staging was done according to the International Federation of Gynecology and Obstetrics (IFGO) 2009 classification.

The Radiologic examinations included:

Post contrast MDCT scan of the chest, abdomen and pelvis on a 64-detector scanner, The IV contrast dose was 1.1 ml/kg body weight. Axial images were obtained with a slice thickness of 0.6 mm. Coronal and sagittal MPR (Multi-Planner Reformat) images were then generated on the workstation.

Post contrast MRI of the pelvis on a 1.5-Tesla scanner with a phased-array pelvic coil. The MRI protocol consisted of axial T1 weighted images; T2 weighted images in the axial, axial oblique and sagittal planes, with or without Diffusion weighted images, following the European Society of Urogenital Radiology recommendations.

All patients received neoadjuvant chemotherapy consisted of cisplatin 75 mg/m^2 (or carboplatin AUC 5) and paclitaxel 175 mg/m^2 on day 1 with the supportive treatment including dexamethasone, chlorpheniramine, ranitidine, ondansetron and aprepitant 30 min before chemotherapy infusion together with proper IV hydration. Chemotherapy was given at 3 weeks interval. A maximum of 3 cycles were given.

Assessment of resectability was done 2 weeks after the 3rd cycle by MRI and examination under anesthesia EUA, patients with tumor localized in the cervix with no parametrial or vaginal extension were considered resectable. Surgically candidate patients were referred for radical hysterectomy after obtaining informed consent, while the rest of patients were directed to receive definitive chemoradiotherapy.

Response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [12].

Chemotherapy Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 [13].

Surgery was performed for the group of patients, who achieved down staging & resectability following NAC, either open or laparoscopic radical hysterectomy was done (type B-C (1-2) Querleu–Morrow radical hysterectomy) [14].

Statistical Analysis

Data were analyzed using SPSS software (version 21). Qualitative

data were expressed as count and percent.

Quantitative data were initially tested for normality using Kolmogorov-Smirnov and Shapiro-Wilk's test with data being normally distributed if (p>0.05). Quantitative data were expressed as mean ± Standard Deviation (SD) or median.

Results

Patients' characteristics are shown in table1.

All patients have completed the 3 courses of chemotherapy. Twenty six patients received paclitaxel, cisplatin chemotherapy, while 11 patients received paclitaxel, carboplatin.

Among the 37 patients treated with neoadjuvant chemotherapy, 29 patients (78.4%) achieved response (CR+PR). Complete response was detected in 7 (18.9%) patients, 22 (59.5%) patients expressed partial response, 8 (21.6%) patients had stable disease; no disease progression was detected in any of the patients with chemotherapy (Table 2). Of the 29 patients (78.4%) who achieved response (CR+PR), 20 (69%) patients (54.1% of the total 37 patients) became resectable & underwent surgery, after a median duration of 3.5 weeks (95% CI: 3-5) from the last cycle of chemotherapy. Most of patients who became resectable were of stage IIb (Table 3).

Radical hysterectomy and pelvic lymphadenectomy was the standard operation, open radical hysterectomy was done in 11 patients, while laparoscopic was done in 9 patients.

Post operative pathologic examination revealed complete pathologic response in 5 (25%) patients & positive LN in 4 (20%) patients of the 20 patients who underwent surgery.

Regarding treatment toxicity, alopecia was the commonest non hematologic toxicity, while anemia & neutropenia were the most common hematologic toxicity (Table 4).

Correlation of prognostic factors (age, PS, stage, tumor size, LN status, histopathologic subtype, keratinized versus non keratinized and tumor grade) with tumor resectability revealed that stage (p<0.001), tumor size (p=0.04) and pathologic type in favor of keratinized (p=0.01), were the most significant factors that affected resectability.

Discussion

Concurrent chemoradiotherapy is the standard treatment for locally advanced cervical carcinoma [12].

The delivery of CCRT needs multiple radiation centers delivering external beam radiotherapy & brachytherapy, which represents an obstacle in developing countries, which may delay treatment delivery, so neoadjuvant chemotherapy represents an alternative treatment option and offers with radical surgery a preliminary local control.

Historically, the rationales of NAC were: (1) inhibition of distant metastasis by eradication of micro metastases, and (2) increasing the rate of both complete pathologic response and radical surgical resection, by tumor cytoreduction, pouring into improvement of loco regional control [15].

The main pattern of recurrence of locally advanced cervical carcinoma has been identified to be loco regional, despite the considerable results of concurrent chemoradiotherapy, new treatment options are needed to improve loco regional control [5].

Table 3: Relation between Staging & Resectability.

Stage	No	Resectability				χ2	P
		Resectable		Non resectable			
		No	%	No	%		
IIb	22	17	77.30%	5	22.70%	19.6	<0.001*
IIIb	12	3	25%	9	75%		
IIIIa	3	0	0%	3	100%		

*Significant

Table 4: Treatment-related toxicity.

Toxicities	Grade I		Grade II		Grade III		Grade IV	
	No	%	No	%	No	%	No	%
Haematological								
Anaemia	13	35.1	6	16.2	3	8.1	0	0
Neutropenia	12	32.4	4	10.8	1	2.7	0	0
Thrombocytopenia	5	13.5	3	8.1	1	2.7	0	0
Non-hematological								
Nausea, Vomiting	11	29.7	5	13.5	0	0	0	0
Neuropathy	0	0	9	24.3	0	0	0	0
Hypersensitivity	4	10.8	3	8.1	0	0	0	0
Alopecia	14	37.8	23	62.2	0	0	0	0

The role of NAC locally advanced cervical carcinoma was limitedly studied [16].

NAC presents a considerable treatment modality for locally advanced cervical carcinoma. It achieved 84% objective response rate, 61.9% 5 year PFS, and 72.8% 5 year OS. Furthermore, NAC showed a mild toxicity [12].

In the current study, from the 37 patients who treated with neoadjuvant chemotherapy, 29 patients (78.4%) achieved response (CR+PR), of them 20 (69%) patients (54.1% of the total 37 patients) became resectable & underwent surgery, regarding treatment toxicity, alopecia was the commonest non hematologic toxicity, while anemia & neutropenia were the most common hematologic toxicity.

In a met analysis by Osman M, to compare the outcomes of neoadjuvant chemotherapy & surgery versus RT for locally advanced cervical carcinoma, he found that NAC-S expressed longer survival for stages IB2-IIB in comparison to stage III [11].

In a prospective trial by Uma et al., they evaluated the role of neoadjuvant chemotherapy in the treatment of locally advanced cervical cancer. NACT achieved down staging in half of the patients after 3 cycles. Complete pathological response was detected in 37.5% of patients [5].

In a retrospective study of 476 patients with stage IB2-IIB cervical carcinoma, treated with NAC plus surgery hada significant higher 5 year overall survival than the surgery (p=0.02) and concurrent chemoradiotherapy (p<0.0001) groups [6].

In a study by Robova et al. [17], a review of 144cervical cancer patients (stage Ib1-Ib2), treated with neoadjuvant chemotherapy revealed that, one hundred thirty-two patients (93.6%) attained response or stable disease & underwent radical hysterectomy.

On the final histopathological examination, CR was present in 16 cases (11.3%) and PR in 98 cases (69.5%). There were positive

lymph nodes in 22 patients (16.7%) of the 132 who underwent surgery. Only 33 patients (25.0%) underwent adjuvant radiotherapy after surgery. Adjuvant chemotherapy was used in 89 cases (67.4%). Hematological toxicity was the most common adverse effect, Grade 3 & 4 neutropenia was found in only 2.1% of the women, Grades 3 & 4 thrombocytopenia in 0.4%, no grades 3 or 4 anemia. Grade 3 & 4 nausea and vomiting in 0.7% [17].

Between 2007 and 2010, 46patients with cervical carcinoma (stage IB2 - IIIB) were included and treated with NAC followed by surgery. The chemotherapy protocol consisted of topotecan (0.75 mg/m^2, D 1-3) and Cisplatin is (75 mg/m^2, D 1). They found a pathological CR in 15.8% of patients. The 2-year PFS and OS were 79% and 95%, respectively [18].

In 2012, the Japanese Gynecologic Oncology Group conducted a phase II trial on 66 patients with stage IB2 to IIB cervical cancer. Patients received irinotecan (60 mg/m^2 on D 1 & 8) and nedaplatin (80 mg/m^2 on D 1) with 3 weeks interval, followed by radical surgery. The response rate was 75.8% which is nearly similar to the current study. Neutropenia was developed in 72.2%, with tolerable adverse effects of NAC [19].

In a retrospective review, 85 patients with FIGO IB–IIB cervical carcinoma treated with NAC+S were compared to 358 control patients treated with CCRT. The NAC+S group expressed down staging and CR were 68.2% and 22.6%, respectively which were close to the present study. The 5-year LCR, PFS, and OS in the NAC+S group were 89.7%, 75.6%, and 92.1%, respectively, which were comparable to 92.5%, 74%, and 84.9% detected in the CCRT group, ($p>0.05$) concluding that, NAC+S was not inferior to standard CCRT, the standard treatment [20].

Further trials showed a higher response rate with NAC, which may be an alternative option for locally advanced cervical cancer [21,22].

Conclusion

In conclusion, neoadjuvant chemotherapy is an efficient and tolerable treatment option in down staging of locally advanced cervical cancer also, it represents plus radical surgery a preliminary local control for locally advanced stages, especially if access to radiation oncology centers is limited with long waiting lists.

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