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Research Article

TREATMENT OUTCOME AND TOXICITY OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CONCOMITANT CHEMORADIOTHERAPY VERSUS CONCOMITANT CHEMORADIATION ALONE IN LOCALLY ADVANCED CERVICAL CARCINOMA: A COMPARATIVE STUDY

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ABSTRACT

Objectives: This study intended to explore the outcome, and toxicities of neoadjuvant chemotherapy in addition to standard treatment concomitant chemoradiation in locally advanced cervix cancer.

Methods: Sixty-two (n=62) locally advanced cervical carcinoma patients were randomized into two arms: The controlled arm (30 patients) received concomitant chemoradiation with external beam radiation therapy of 50 Gy to the whole pelvis and Inj. Cisplatin (40 mg/m^2/week) alone and the study arm (32 patients) received three cycles, neoadjuvant chemotherapy with Inj. Paclitaxel (175 mg/m^2), and Inj. Cisplatin (75 mg/m^2) at 3 weekly intervals, followed by concomitant chemoradiation with external beam radiation therapy (EBRT) of 50 Gy to whole pelvis and Inj. Cisplatin (40 mg/m^2/week). Responses to treatment, toxicities, disease-free survival, and progression-free survival (PFS) were analyzed in both arms.

Results: Among the total of 62 patients, 30 were in the concomitant chemoradiation alone arm and 32 were in neoadjuvant chemotherapy followed by the concomitant chemoradiation arm. The median follow-up period was about 13 months. The tumor response in the form of complete or partial responses was equivalent in the two arms. The disease-free survival and the PFS were also comparable in both arms. The acute and the late toxicities were also comparable in the two arms.

Conclusions: This study showed that neoadjuvant chemotherapy with paclitaxel and cisplatin before definitive concomitant cisplatin-based chemoradiation can be used as an alternative in the management of locally advanced carcinoma of the cervix.

Keywords: Neoadjuvant chemotherapy, Locally advanced, Cervical cancer.

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INTRODUCTION

Cervical cancer is one of the leading causes of cancer death among women worldwide. The 2nd most common cancer in women in India is cancer of the cervix. Concurrent radiotherapy is the primary local treatment for patients with stages IIB, III, and IVA disease (locoregionally advanced cervical carcinomas) [1-3]. The outlook for such patients remains poor and new approaches are needed. For this reason, neoadjuvant chemotherapy (NACT) comes into the picture. While concurrent chemotherapy given with radiation tends to increase the radiosensitivity of the tumor, NACT given before CRT is likely to reduce the size of bulky tumors and control the micrometastatic disease. The role of concurrent chemoradiation has already been established in the treatment of locally advanced disease, while the role of neoadjuvant chemotherapy is still being investigated. To date, trials addressing the role of NACT have generated conflicting data. Several phase III randomized trials comparing radiation alone with NACT followed by definitive radiation in locally advanced cervical cancer show no advantage in terms of response and overall survival [4–7]. One study reported better survival rates for the neoadjuvant chemotherapy arm, using several combinations of chemotherapy based on cisplatin in patients with stages IB2-IIIB [8]. In this study, the benefit derived only reached statistical significance for stages IB and IIB patients. The main limitations of these earlier studies were that the comparisons were made relative to radiation alone and not concurrent cisplatin-based chemoradiation which at present, which is the standard of treatment. Neoadjuvant chemotherapy followed by concurrent chemoradiation has been compared to concurrent chemoradiation alone (which is the present standard of care) in locally advanced carcinoma of the cervix, which showed encouraging results for the use of neoadjuvant chemotherapy [9-10]. However, there are little data to believe that adding neoadjuvant chemotherapy might result in better tumor control, leading to increased overall survival than with concurrent chemotherapy alone with added risks of slightly enhanced toxicity. Neoadjuvant chemotherapy given before concomitant chemoradiation may reduce tumor size and control the micrometastatic disease. It might downstage tumors, lengthen exposure to systemic therapy, and improve outcomes in more advanced diseases or large tumors. This study aims to find the impact of the addition of NACT to standard concomitant CRT, in terms of survival and acute and late toxicities in the treatment of locally advanced carcinoma of the cervix, and compare it with the concomitant CRT alone.

METHODS

After obtaining approval from the Institutional Ethics Committee (IEC), sixty-two (n=62) histologically confirmed squamous cell carcinoma of cervix locally advanced stage (FIGO-stage IIB to IVA.) with ECOG performance status 0–2 were included for single institutional, prospective, interventional, open-labeled, and randomized study. After the initial investigative workup, patients were randomized into two arms: The controlled arm (30 patients) received concomitant chemoradiation with external beam radiation therapy (EBRT) of 50 Gy to the whole pelvis and Inj. Cisplatin (40 mg/m^2/week) and 7 Gy in three fractions intracavitary brachytherapy alone and study arm (32 patients) received three cycles, neoadjuvant chemotherapy with Inj. Paclitaxel (175mg/m^2) intravenous on day-1 and Inj. Cisplatin (75 mg/m^2) IV on day-2, at 3 weekly intervals, followed by concomitant chemoradiation

with external beam radiation therapy (EBRT) of 50 Gy to whole pelvis and Inj. Cisplatin (40 mg/m^2/week) and 7 Gy in 3 fractions intracavitary brachytherapy. All patients received radiotherapy in a supine position with proper immobilization in cobalt 60-ATC-C9 (picker manufacture). Standard conventional 2-D 4 field box technique used for radiotherapy treatment planning. Pre- and post-treatment data are collected in a case record form with the help of history taking, detailed clinical examination, radiological assessment, and laboratory investigations. Data were collected during the pre-treatment check-up and treatment period. Then, in the post-treatment period, follow-up of patients was done every month for the initial 3 months after completion of treatment and thereafter at an interval of 3 months until the end of the study. Responses to treatment, toxicities, disease-free survival (for complete responders), and progression-free survival (PFS) (for partial responders and stable disease) were analyzed in both arms. The median follow-up for this study was 13 months (range, 6–18). Disease-free survival was obtained using the Kaplan–Meier survival curve. PFS was measured among the non-CR group after completion of treatment until the date of the last follow-up visit. Kaplan–Meier survival estimate plot was also drawn for PFS.

RESULTS

Age and the performance status of the patients in both arms are comparable with p-value of 0.996 and 0.892, respectively. Among 62 total patients, 28 (45%), 7 (11%), and 27 (44%) patients were of FIGO stage IIB, IIIA, and IIIB, respectively. There was no Stage IVA patient (Table 1). The treatment time factors were comparable in both arms (Table 2). Although acute and late toxicities as observed were higher in arm 2 receiving NACCT and CRT, the differences were however not statistically (details of acute and late toxicities were depicted in Tables 3-5). The median follow-up period was about 13 months. There were 46 complete responders in the study. The difference in DFS (disease-free survival) is statistically not significant between the two arms, with log rank test p=0.882. The median DFS of the entire population is 8 months (Fig. 1); SD-3.13 (interquartile range 6–11). Mean DFS is 9 months (95% CI 13.83––15.17). There were 16 non-complete responders in the study. Of them, 15 showed partial response (PR) and one showed stable disease (SD). The PFS between the two arms is also comparable, p=0.655. The median PFS of the entire population is 6 months (Fig. 2); SD=1.20 (interquartile range 4–6). The mean PFS is 5.56 months (95% CI 6.62–8.04).

Table 1: FIGO staging (n=62) distribution in two arms

ARM	FIGO stage			Total	p value
	IIB	IIIA	IIIB		Chi-square
1	13	3	14	30	0.878
2	15	4	13	32	

DISCUSSION

In the decade since the introduction of chemoradiation therapy, there have been no further advances in the management of locally advanced cervical carcinoma except for the introduction of three-dimensional image-based brachytherapy, which is still out of reach of most of the Indian population due to technological challenges. The role of neoadjuvant chemotherapy in cervical carcinoma has been examined in several trials, but its role remains yet to be defined. The rationale for giving neoadjuvant chemotherapy in the setting of locally advanced carcinoma cervix is that it results in the down-staging of the tumor. This is particularly important in bulky tumors of the cervix, that is, >4 cm in size, where the response rate with concurrent chemoradiation is not satisfactory. This is probably because these tumors have a central hypoxic zone and as we know that these hypoxic cells in a tumor have inherent radio resistance. Hence, if we can reduce the size of the tumor with neoadjuvant chemotherapy and result in proper oxygenation of the tumor cells, the radiation therapy given following that will be more effective. This is expected to help in better local control of the disease. Down-staging of the tumor by neoadjuvant chemotherapy may also help in reducing the bulk of the parametrial disease, thereby reducing parametrial recurrence. It may also control the occult micrometastatic disease. This is important in reducing para-aortic lymph node and distant recurrence. However, the disadvantage of neoadjuvant chemotherapy is that if the disease does not respond to the given regimen, it will result in a delay in the institution of definitive therapy with the risk of disease progression.

It was seen that when surgery was used to consolidate the treatment following neoadjuvant chemotherapy, the results were better. This is supported by several phase II trials like the studies conducted, using neoadjuvant chemotherapy, which reported a longer overall survival in three separate studies involving stages IB2, IIB, and IIIB patients [11-13]. There were six such phase III trials, all of which showed no advantage of neoadjuvant chemotherapy either in terms of response or overall survival [14-19]. In all these studies, neoadjuvant chemotherapy was either followed by pelvic radiotherapy alone or by surgery in cases of locally advanced carcinoma of the cervix. However, to prove the role of neoadjuvant chemotherapy, it needs to be followed by the standard therapy of locally advanced cervical carcinoma, which is concurrent chemoradiotherapy and has to be compared to concurrent chemoradiation alone.

Two recent works have compared this modality of treatment with concurrent chemoradiation in locally advanced cervical

Table 2: Treatment time factors for the treatment arms

Treatment time parameters (radiotherapy)	Group	Mean	Standard deviation	Standard error mean	p-value	Standard deviation	Variance
Total days	Arm 1 (n=30)	36.23	2.373	0.433	0.281	2.216	4.910
	Arm 2 (n=32)	36.75	2.064	0.365			
Treatment gap	Arm 1 (n=30)	3.23	2.373	0.433	0.281	2.216	4.910
	Arm 2 (n=32)	3.75	2.064	0.365			
Total treatment duration	Arm 1 (n=30)	59.9	3.595	0.656	3.633	28.61	818.541
	Arm 2 (n=32)	116.25	3.547	0.627			

Table 3: Acute hematological toxicity

Acute hematological Toxicity	Toxicity		Toxicity		p value Fisher's exact test
	Grade – 2	Grade – 3	Grade – 0	Grade – 1	
	ARM 1 (N=30)	ARM 2 (N=32)	ARM 1 (N=30)	ARM 2 (N=32)	
Anemia	10 (33.33%)	15 (46.87%)	20 (66.66%)	17 (53.12%)	0.310
Neutropenia	8 (26.66%)	11 (34.37%)	22 (73.33%)	21 (65.62%)	0.587

Table 4: Acute upper and lower GI toxicity

Grades of toxicity	ARMS		Total	p value Chi-square
	1	2		
Upper GI				
0	12	5	17	0.127
1	10	17	27	
2	8	9	17	
3	0	1	1	
Lower GI				
0	14	15	29	0.670
1	12	10	22	
2	4	6	10	
3	0	1	1	

GI: Gastrointestinal

Table 5: Late toxicity

Grades of toxicity	Arm-1	Arm-2	Total	p-value
Intestine				0.355
0	26	25	51	
1	4	5	9	
2	0	2	2	
Bladder				0.524
0	29	30	59	
1	1	2	3	
Skin				1.00
0	27	28	55	
1	3	4	7	

carcinoma [20,21]. Their studies have shown positive results concerning the use of neoadjuvant chemotherapy in this setting. In one study [10], the complete response rates noted were 97% and 87% in the neoadjuvant group and the chemoradiation group, respectively. There were no differences in overall survival between the two arms. In another single-arm phase II trial, the response rates were 70% post-NACT and 85% post-CRT. The overall and PFSs at 3 years were 67% and 68%, respectively [11]. Grade 3/4 toxicities were 20% during NACT and 52% during CRT. In the present study, the two treatment modalities, one NACT followed by concurrent chemoradiation, and the other, concurrent chemoradiation alone in locally advanced carcinoma of the cervix were compared. The neoadjuvant chemotherapy was given with Inj. Paclitaxel (175mg/m^2) IV on day one over 3 h infusion and Inj. Cisplatin (75 mg/m^2) IV on day two, with adequate premedication, proper hydration, anti-emetic treatments, and adequate diuretic support. The regimen was administered at an interval of 3 weeks (21 days), for three cycles. The combination of taxane and platinum is known to be active in advanced and recurrent cervical cancer with response rates of 40–50%. This combination is also active in the neoadjuvant setting with reported response rates of up to 90–95% [22]. Cisplatin and paclitaxel require a longer infusion compared with the carboplatin/paclitaxel combination, which is demonstrated to have acceptable toxicity and promising activity [4,5].

The locoregional control of the disease in terms of CR or PR was comparable to the two arms in our study, with p=0.579. The overall response rates (CR+PR) in Arm 1 (chemoradiation alone arm) and Arm 2 (neoadjuvant chemotherapy followed by chemoradiation arm) were 96% and 100%, respectively (complete response rates of 73.33% and 75%, respectively, and the partial response rates of 23.33% and 25%, respectively). The results were, therefore, similar to the reported literature [9,10]. The complete response rate was 87% and 97% in the chemoradiation alone arm and neoadjuvant followed by the definitive chemoradiation arm, respectively. The disease-free survival (DFS) among the complete responders and the PFS among the non-complete

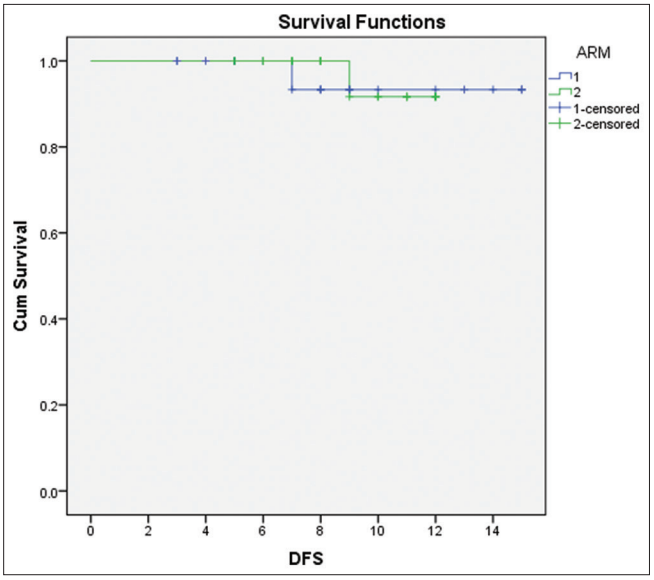

Fig. 1: Kaplan–Meier plot showing disease-free survival probability in two study arms (log-rank test p=0.882)

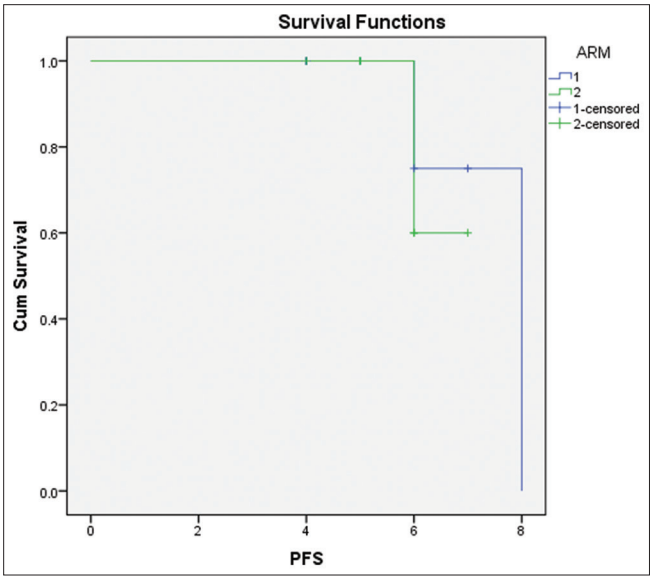

Fig. 2: Kaplan–Meier plot progression-free survival comparison between two arms (log-rank test p=0.655)

responders (partial response and stable disease) were again comparable between the two arms (p=0.882 and 0.655, respectively). Regarding acute toxicities, it was only acute nephrotoxicity that achieved a statistically significant difference between the two arms (p=0.021) with higher toxicity being observed in the neoadjuvant arm, other acute and late toxicities were found to be comparable in both the arms with no statistically significant differences. The chemoradiation part of both the arms was similar – the patients received EBRT (Cobalt^{60}) to the whole pelvis up to a dose of 50 Gy in 25 fractions over 5 weeks, along with weekly concomitant Cisplatin (40 mg/m^2) and then HDR intracavitary Brachytherapy (by Iridium^{192}) to deliver 21 Gy to point A in 3 fractions (7 Gy/fraction). The confounding factors such as age distribution, stage distribution, grade-wise distribution, ECOG performance status, parity of the patients, and the meantime of follow-up between the patients of the two arms were comparable in this study.

The results of this study indicate that neoadjuvant chemotherapy with paclitaxel and cisplatin followed by definitive cisplatin-based

concurrent chemoradiation is at least as effective as standard cisplatin-based chemoradiation alone in the treatment of locally advanced carcinoma of the cervix in terms of response and survival. The response was observed to be better with the addition of neoadjuvant chemotherapy, although the difference did not achieve statistical significance. The toxicity was however amenable to correction with conservative management. Hence, it can be said that a good response rate is achievable with acceptable toxicity by NACT with paclitaxel and cisplatin followed by radical concurrent chemoradiation therapy when compared to standard chemoradiation therapy alone. This modality of treatment therefore can be used as an alternative in the management of locally advanced carcinoma of the cervix, especially in those patients who have the bulky local disease (to reduce local recurrence) and those who are at particularly high risk of para-aortic lymph node metastasis (to reduce systemic recurrence). In this subgroup of patients, the results with concomitant chemoradiation alone have been poor and the addition of neoadjuvant chemotherapy appears to improve the disease outcome. It is also helpful in a country like India, where the load of cancer cervix is high and a long waiting period for radiation therapy usually exists.

However, there were some limitations to our study. Our sample size was small, so any statistical data have to be interpreted with caution. It was a single institutional study; hence, results derived cannot be extrapolated to the entire population. Some other contributing factors like nutritional status and fall in the quality of life are not adjusted for assessing the response rate and disease-free survival.

CONCLUSIONS

This study showed that neoadjuvant chemotherapy with paclitaxel and cisplatin before definitive concomitant cisplatin-based chemoradiation can be used as an alternative in the management of locally advanced carcinoma of the cervix, especially in those patients who have the bulky local disease (to reduce local recurrence) and those who are particularly at high risk of para-aortic lymph node metastasis (to reduce systemic recurrence). In this subgroup of patients, the results with concomitant chemoradiation alone have been poor and the addition of neoadjuvant chemotherapy appears to improve the disease outcome producing a good response with acceptable toxicity.

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AUTHORS' CONTRIBUTIONS

All authors contributed equally to this article including data collection, manuscript writing, and reviewing statistical analysis.

CONFLICTS OF INTEREST

All author declares that there are no conflicts of interest for the publication of this article.

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