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RESEARCH ARTICLE

Effect of concurrent chemoradiation with cisplatin versus concurrent chemoradiation with carboplatin in locally advanced carcinoma cervix: A quasi-experimental study

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Abstract

Background: The standard approach for locally advanced cervical cancer is concurrent chemoradiation with platinum agents, preferably cisplatin. This study was aimed at comparing the treatment response and toxicity of carboplatin-based versus cisplatin-based concurrent chemoradiation in locally advanced carcinoma of the cervix.

Methods: This quasi-experimental study was conducted from September 2022 to August 2023 on 80 patients with locally advanced carcinoma cervix. Patients were divided evenly between the two arms (40 in each Arm). Arm A received weekly cisplatin 40 mg/m², while Arm B received weekly carboplatin with an area under the curve equal to 2 during external beam radiation. Then all the patients in both arms were treated by intracavity brachytherapy. Each patient was evaluated weekly during treatment and three months after the completion to assess treatment response and treatment related acute toxicities.

Results: After three months of completion of treatment, the response was statistically similar between arms [Arm A, 35 (87.5%) versus Arm B, 37 (92.5%), *P*=0.71]. In terms of toxicity, Arm B had significantly less anaemia (*P*=0.03), vomiting (*P*=0.05), and renal toxicity (*P*=0.03) than Arm A. Other toxicities such as leucopenia, thrombocytopenia, nausea, hyponatremia, radiation-induced dermatitis, cystitis, proctitis, and diarrhea were similar between arms.

Conclusion: Concurrent chemoradiotherapy with carboplatin had a similar therapeutic response to concurrent chemoradiotherapy with cisplatin in locally advanced cervical cancer. Furthermore, the carboplatin arm had lesser toxicity than the cisplatin arm in terms of anaemia, vomiting, and renal toxicity.

Key messages

In the case of locally advanced carcinoma cervix, the use of concurrent chemoradiation with carboplatin had a similar treatment response to cisplatin-based concurrent chemoradiation. Concurrent chemoradiation with carboplatin had less chance of anaemia, vomiting, and renal toxicity. Toxicities such as leucopenia, thrombocytopenia, nausea, hyponatremia, radiation-induced dermatitis, cystitis, proctitis, and diarrhea were similar between carboplatin and cisplatin-based concurrent chemoradiotherapy.

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Introduction

Cervical carcinoma is the most common gynecological malignancy and is considered a major global health problem for women. It is the eighth most common cancer in the world, with an anticipated 6,04,127 cases and 3,41,831 deaths in 2020, according to the Global Cancer Observatory (GLOBOCAN) 2020 database. The incidences of cervical cancer are significantly higher in underdeveloped countries such as Sub-Saharan Africa and Southeast Asia [1]. In Bangladesh, according to the hospital cancer registry report (2018-2020), carcinoma cervix is the 2nd most common malignancy among the female population of Bangladesh [2]. The three most prevalent histologies of cervical cancer are squamous cell carcinoma (SCC), adenocarcinoma (AC), and small cell neuroendocrine carcinoma. SCC accounts for approximately 80% and AC accounts for approximately 20% of all cervical cancers [3].

Asian countries exhibit a higher prevalence of locally advanced carcinoma cervix (LACC) [4]. According to a Bangladeshi study, the majority of these patients had stage IIB disease [5]. The treatment options for cervical cancer are composed of surgery, radiotherapy, and/or chemotherapy according to the stage and performance status of patients. Radiotherapy plays a vital role in the management of LACC. Both external beam radiation therapy (EBRT) and intracavitary brachytherapy (ICRT) are used as radiotherapy. According to the National Comprehensive Cancer Network (NCCN) guideline, the recommended treatment choice for locally advanced carcinoma cervix is concurrent chemoradiation (CCRT), which includes pelvic external beam radiotherapy concurrent with platinum agents, preferably cisplatin, followed by intracavity brachytherapy [6]. Cisplatin-based CCRT is the preferred treatment option because of its established benefits in terms of overall survival and progression-free survival compared to radiotherapy alone [7, 8].

Cisplatin is a platinum complex that acts as DNA cross-linkers and reacts preferentially with N-7 guanine and blocks DNA replication, RNA transcription, and protein synthesis. Despite its proven benefit, cisplatin-induced toxicity such as nausea, vomiting, nephrotoxicity, and neurotoxicity are common, and a specific hydration policy is needed to be maintained during cisplatin administration. Carboplatin, on the other hand, is another platinum-based chemotherapy that has a similar mechanism of action as cisplatin. Compared to cisplatin, carboplatin rarely causes nephrotoxicity or severe nausea or vomiting; instead, its dose-limiting toxicity is myelosuppression, primarily thrombocytopenia [9]. In a Thai study, carboplatin showed equivalent outcomes to cisplatin in concurrent chemoradiation for locally advanced cervical cancer. Furthermore, carboplatin was associated with higher compliance and lower rates of anemia, neutropenia, and nephrotoxicity [10]. Therefore, carboplatin is often used instead of cisplatin in patients who are unable to tolerate cisplatin-related toxicity or the aggressive hydration that needs to be avoided. Since no previous study was carried out to compare the effectiveness of these two-platinum based anticancer drugs during concurrent chemoradiation of cervical cancer in our country's perspective, the present study may aid in optimising the concurrent chemoradiation schedule in cervical cancer in Bangladesh. The objective of the study was to compare the treatment response and toxicity of concurrent chemoradiation with carboplatin to concurrent chemoradiation with cisplatin in LACC.

Methods

Design and sample size calculation

This was a quasi-experimental study and the total sample size was 84. We need 36 patients in each arm according to the following formula:

$$n = \frac{p1(1-p1) + p2(1-p2)}{(p1-p2)2} \times (Z\alpha + Z\beta)^2$$

where, p1= 0.35, p2=0.066, Zα=1.96, Zβ= 1.28 [10, 11, 12]. With 10% allowance for lost to follow up, final sample size was 40 in each arm.

Selection criteria of patients

Criteria for inclusion

Biopsy-proven squamous cell carcinoma or adeno-carcinoma of the cervix in a locally advanced stage (Stage IIB to IVA).

Criteria for exclusion

Age below 20 and above 70 years old; other epithelial tumors of the cervix, including neuroendocrine tumors; patients with an Eastern Co-operative Oncology Group (ECOG) performance status of three or above; prior chemotherapy or pelvic radiation or surgery; uncontrolled concurrent medical condition; and pregnant or lactating patients were excluded.

Study design and treatment

The study was conducted from September 2022 to August 2023 at Bangabandhu Sheikh Mujib Medical University (BSMMU), Delta Hospital Limited, and Ahsania Mission Cancer and General Hospital in Dhaka, Bangladesh. At first, a total of 91 patients of LACC was assessed for eligibility. Seven patients were excluded as they did not meet selection criteria. Finally, following the application of inclusion and exclusion criteria, 84 patients were equally divided between two arms (42 patients in Arm A and 42 patients in Arm B) using purposive sampling (Figure 1). Two patients from each arm were either dropped or lost to follow up. Finally, 40 participants in each arm were analysed.

Patients of Arm A were treated by concurrent chemoradiation (CCRT) with weekly cisplatin at a dose of 40 mg/m² intravenously. Patients of Arm B were treated by concurrent chemoradiation (CCRT) with weekly carboplatin intravenously at a dose of Area Under the Curve (AUC) equal to 2 using the Calvert formula. As a part of CCRT, all patients received pelvic radiotherapy to the primary tumor and pelvic lymph nodes at a total dose of 50 Gy in 25 fractions by the three-dimensional conformal radiation therapy technique. After pelvic radiation with EBRT, all the patients of both arms were treated with ICRT. Three insertions (one insertion per week) of ICRT and 7 Gy for each insertion were given.

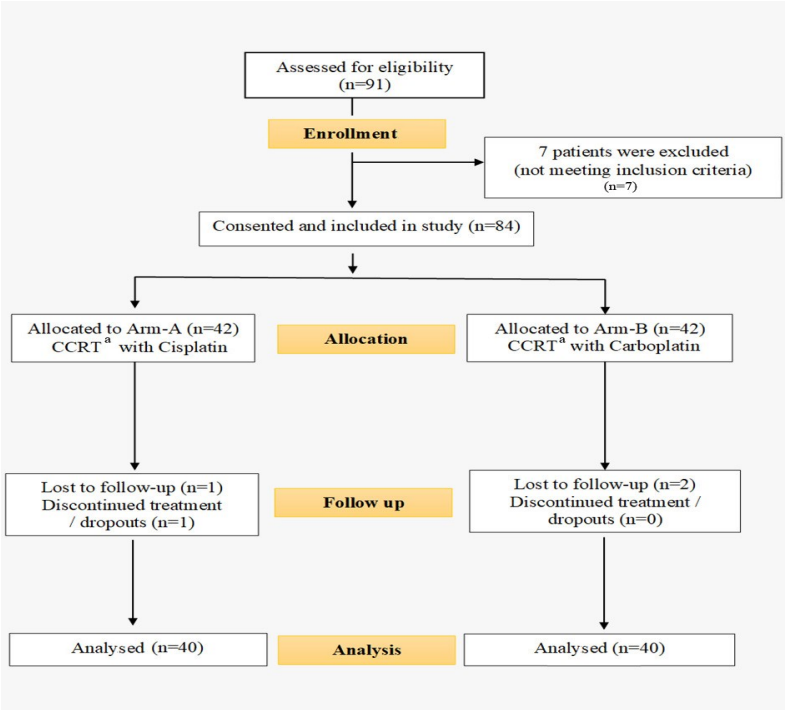

Figure 1 Concurrent chemoradiative patient enrollment, allocation, follow-up, and analysis

[a]CCRT indicates concurrent chemoradiation

Assessment and data collection

In this study, outcome variables are treatment responses and acute toxicities. Patients of both arms were assessed weekly during CCRT, starting from the onset of radiotherapy. Response evaluation was done during and after treatment. The final responses were documented 3 months after completion of all therapy. To assess the tumor response to the radiotherapy treatment, Response Evaluation Criteria in Solid Tumors (RECIST) were followed [13]. According to RECIST criteria, if there is complete disappearance of all target lesions, it is mentioned as complete response (CR), if there is 30% or more reduction of size of all target lesions it is mentioned as partial response (PR), 20% or more increase size of target lesions is mentioned as progressive disease (PD) and finding in-between PR and PD is stated as stable disease (SD). Acute and late hematological toxicities (both hematological and non-hematological), if present, were recorded using toxicity criteria of the radiation therapy oncology group [14]. To gather information, a data collection sheet was employed.

Table 1 Characteristics of the concurrent chemoradiative patients

Characteristics	Total (n=80)	Arm A (CCRT[b] with Cisplatin) (n=40)	Arm B (CCRT[b] with Carboplatin) (n=40)	*P*
Age (years), mean (SD)[a]	51.5 (9.1)	52.0 (8.8)	50.9 (9.4)	0.59
ECOG Performance Status				
ECOG 0	62 (77.5)	32 (80.0)	30 (75.0)	0.84
ECOG 1	14 (17.5)	6 (15.0)	8 (20.0)	
ECOG 2	4 (5.0)	2 (5.0)	2 (5.0)	
Stage				
Stage IIB	44 (55.0)	23 (57.5)	21 (52.5)	0.96
Stage IIIA	3 (3.8)	2 (5.0)	1 (2.5)	
Stage IIIB	7 (8.8)	3 (7.5)	4 (10.0)	
Stage IIIC	9 (11.3)	4 (10.0)	5 (12.5)	
Stage IVA	17 (21.3)	8 (20.0)	9 (22.5)	
Histological type				
Squamous cell carcinoma	73 (91.3)	37 (92.5)	36 (90.0)	0.99
Adenocarcinoma	7 (8.8)	3 (7.5)	4 (8.8)	
Histological differentiation				
Well differentiated	11 (13.8)	5 (12.5)	6 (15.0)	0.87
Moderately differentiated	60 (80.0)	31 (77.5)	29 (72.5)	
Poorly differentiated	9 (11.3)	4 (10.0)	5 (12.5)	

[a]Age in mean and standard deviation, all others are number (%); [b]CCRT indicates concurrent chemoradiation

Ethical considerations

After Institutional Review Board (IRB) approval from BSMMU, permission was taken from Department of Clinical oncology, BSMMU, Delta Hospital Limited, and Ahsania Mission Cancer and General Hospital in Dhaka, Bangladesh. The study was carried out in line with the Helsinki Declaration and good clinical practice guidelines. All patients were given an explanation of the study, including the risks and benefits. They were also informed that if any complication arises due to the intervention, they will avail treatment for that particular complication free of cost. It was also explained to them that they have the right to refuse or accept to participate in the study. Before each patient's involvement in the study, signed informed consent was obtained from them. All data obtained during the study period from the patient was kept confidential.

Table 2 Assessment of treatment response at three months after completion of treatment

Treatment Response	Total (n=80)	Arm A (CCRT[c] with Cisplatin) (n=40)	Arm B (CCRT[c] with Carboplatin) (n=40)	*P*
Complete Response[a]	72 (90.0)	35 (87.5)	37 (92.5)	0.71
Partial Response[b]	8 (10.0)	5 (12.5)	3 (7.5)	

[a]Complete disappearance of all target lesions as per RECIST criteria; [b]30% or more reduction of size of all target lesions as per RECIST criteria; [c]CCRT indicates concurrent chemoradiation

Statistical analysis

Data analysis was done according to the objectives of the study using the SPSS (Statistical Package for Social Science) software program for Windows, version 26.0. In this study, quantitative variables (age) were compared by the *t* test and qualitative variables were compared by fisher's exact test. The results of the test were *P* less than 0.05 was considered statistically significant. Two patients in each arm did not complete the treatment or were lost to follow up (Figure 1). Therefore, 40 patients were analysed per-protocol in each arm.

Locally advanced carcinoma cervix

According to the International Federation of Gynecology and Obstetrics (FIGO), LACC is defined as stages IIB–IVA, which is assessed by clinical examination, imaging and pathological findings.

Results

The mean (standard deviation) of age of the 80 participants in both arms was 51.5 (9.1) years. In Arm A, the mean age was 52 (8.8) years, while in Arm B, the

Table 3 Assessment of treatment response at 3 months after completion of treatment

GIT toxicity	Total (n=80)	Arm A (CCRT[a] with Cisplatin) (n=40)	Arm B (CCRT[a] with Carboplatin) (n=40)	*P*
Nausea				
Grade 0	58 (72.5)	25 (62.5)	33 (82.5)	0.06
Grade 1	15 (18.8)	9 (22.5)	6 (15.0)	
Grade 2	7 (8.8)	6 (15.0)	1 (2.5)	
Vomiting				
Grade 0	71 (88.8)	32 (80.0)	39 (97.5)	0.046
Grade 1	6 (7.5)	5 (12.5)	1 (2.5)	
Grade 2	3 (7.5)	3 (7.5)	0 (0)	
Proctitis				
Grade 0	71 (88.8)	35 (87.5)	36 (90.0)	0.99
Grade 1	5 (6.3)	3 (7.5)	2 (5.0)	
Grade 2	4 (5.0)	02 (5.0)	2 (5.0)	
Diarrhea				
Grade 0	67 (83.8)	33 (82.5)	34 (85.0)	0.82
Grade 1	8 (10.0)	5 (12.5)	3 (7.5)	
Grade 2	5 (6.3)	2 (5.0)	3 (7.5)	

[a]CCRT indicates concurrent chemoradiation

mean age was 50.9 (9.4) years. Nearly two-thirds of all participants (77.5%) had an ECOG performance status score of 0. The majority of the patients in both arms were at stage IIB, with 57.5% in Arm A and 52.5% in Arm B. The vast majority of the patients in both arms were diagnosed with squamous cell carcinoma: 92.5% and 90% for Arms A and B, respectively. Most of the patients in both arms had the histology of a moderately differentiated tumor (77.5% and 72.5% in Arms A and B, respectively) (Table 1).

Final treatment response was evaluated 3 months after completion of treatment by using RECIST criteria. In the final evaluation, a complete response was seen in 35 patients of Arm A and 37 patients of Arm B. Five patients in Arm A and 3 patients in Arm B had partial responses. There was no statistical difference between these treatment responses in both arms (*P*=0.71) (Table 2).

Regarding hematological toxicity, the severity of anaemia was higher in Arm A compared to Arm B. Seven, 9, and 2 patients in Arm A developed grade 1, grade 2, and grade 3 anaemia, respectively, whereas 6 and 2 patients in Arm B developed grade 1, grade 2 anemia, respectively. This finding was statistically significant between the two arms (*P*=0.03). Regarding leucopenia and thrombocytopenia, Arm A had a higher prevalence of leucopenia of all grades, whereas Arm B had a higher prevalence of thrombocytopenia. However, these findings were not statistically significant between the two arms.

In terms of Gastrointestinal tract (GIT) toxicity, there was a higher prevalence of nausea and vomiting in Arm A. Three patients and 5 patients in arm A experienced grade 1 and grade 2 vomiting, respectively. One patient experienced grade 1 vomiting in Arm B. There were no grade 2 vomiting episodes in Arm B. This finding was statistically significant between the two arms (*P*=0.046). Proctitis and diarrhea were two other GIT toxicities that were observed in both groups; however, the findings did not reach statistical significance (Table 3).

In respect of renal toxicity, Grade 1 renal toxicity was seen more in Arm A. 8 patients in Arm A and 1 patient in Arm B developed grade 1 renal toxicity. This finding was statistically significant between the two arms (*P*=0.03). On the other hand, there was almost the same distribution of dermatitis, cystitis, and hyponatremia in both groups (Table 4).

Table 4 Non-GIT toxicities during treatment in both arms

Hematological toxicities	Total (n=80)	Arm A (CCRT[a] with Cisplatin) (n=40)	Arm B (CCRT[a] with Carboplatin) (n=40)	*P*
Anaemia				
Grade 0	54 (67.5)	22 (55.0)	32 (80.0)	0.03
Grade 1	13 (16.3)	7 (17.5)	6 (15.0)	
Grade 2	11 (13.8)	9 (22.5)	2 (5.0)	
Grade 3	2 (2.5)	2 (5.0)	0 (0.0)	
Leucopenia				
Grade 0	55 (68.8)	24 (60.0)	31 (77.5)	0.16
Grade 1	12 (15.0)	6 (15.0)	6 (15.0)	
Grade 2	10 (12.5)	8 (20.0)	2 (5.0)	
Grade 3	3 (3.8)	2 (5.0)	1 (2.5)	
Thrombocytopenia				
Grade 0	62 (77.5)	35 (87.5)	27 (67.5)	0.11
Grade 1	14 (17.5)	4 (10.0)	10 (25.0)	
Grade 2	4 (5.0)	1 (2.5)	3 (7.5)	
Hyponatremia				
Grade 0	70 (85.0)	34 (85.0)	36 (90.0)	0.78
Grade 1	7 (10.0)	4 (10.0)	3 (7.5)	
Grade 2	3 (5.0)	2 (5.0)	1 (2.5)	
Renal toxicity				
Grade 0	71 (88.8)	32 (80.0)	39 (97.5)	0.03
Grade 1	9 (11.3)	8 (20.0)	1 (2.5)	
Dermatitis				
Grade 0	73 (91.3)	37 (92.5)	36 (90.0)	0.99
Grade 1	4 (5.0)	2 (5.0)	2 (5.0)	
Grade 2	3 (3.8)	1 (2.5)	2 (5.0)	
Cystitis				
Grade 0	75 (93.8)	38 (95.0)	37 (92.0)	0.99
Grade 1	5 (6.3)	2 (5.0)	3 (7.5)	

[a]CCRT indicates concurrent chemoradiation

Discussion

CCRT with cisplatin is the current standard in the treatment of LACC because it showed therapeutic benefits compared to radiotherapy alone in various clinical trials [15, 16, 17]. However, many patients cannot receive cisplatin, especially due to pre-existing renal impairment. Therefore, several chemotherapeutic agents that have less nephrotoxicity, including carboplatin, has been investigated during CCRT. In this study, we compared the treatment response and toxicity of carboplatin with cisplatin during CCRT in LACC patients.

In our study, we found that treatment responses in LACC patients were similar in both arms at 3 months after completion of treatment. The complete response rate in Arm A was 87.5%, whereas the complete response rate in Arm B was 92.5%. Several studies showed that carboplatin and cisplatin based CCRT had comparable locoregional control [10, 18, 19]. A retrospective observational study involving 250 patients, 121 in the carboplatin- and 129 in the cisplatin-based CCRT, was carried out by Valdiviezo *et al.* in 2016. They observed that the cisplatin arm had a complete response rate of 85%, while the carboplatin arm had a complete response rate of 71% [20]. A study conducted by Katanyoo *et al.* on 148 carcinoma cervix patients found that carboplatin-based CCRT had a complete response rate of 95.9% [21]. Both studies used the same dose of carboplatin concurrently with EBRT as our study used.

The main reason to consider carboplatin over cisplatin during CCRT is its toxicity profile. Cisplatin, a platinum drug, can produce severe nephrotoxicity,

nausea, vomiting, and myelosupression [22]. Carboplatin, another platinum drug, is widely used to substitute cisplatin due to its comparable mechanism of action but reduced rates of toxicity, notably nephrotoxicity. In this study, we observed that carboplatin-based CCRT had significantly less anaemia, vomiting, and renal toxicity compared to cisplatin-based CCRT, while leucopenia, thrombocytopenia, nausea, hyponatremia, dermatitis, cystitis, proctitis, and diarrhea were not statistically different between two arms. A study conducted by Tharavichitkul *et al.* found that carboplatin significantly reduced anaemia and nephrotoxicity compared to cisplatin during CCRT, which is consistent with our findings. However, the trial found almost similar incidences of vomiting between the two groups, which does not correlate with our observation, possibly due to different antiemetic protocols prior to chemotherapy administration [10]. According to *Kim et al.,* carboplatin showed a higher rate of thrombocytopenia compared to cisplatin [22]. In our study, we also observed that thrombocytopenia developed more commonly in the carboplatin arm than the cisplatin arm, though this finding was not statistically significant between the two arms. Three patients in Arm A and two in Arm B experienced a one -week treatment interruption during CCRT due to toxicities. In cases of treatment interrupted patients, a gap correction of the planned radiotherapy schedule was done.

This study has some limitations. As the period of study was one-year, overall survival or late toxicities could not be evaluated. It was an unblinded, non-randomised, and quasi-experimental study so that selection bias could not be avoided.

Conclusion

In this study, the use of CCRT with carboplatin resulted in a comparable treatment response to cisplatin in LACC. In terms of toxicity, the carboplatin arm showed considerably lower rates of anaemia, vomiting, and renal toxicity than the cisplatin arm. Therefore, carboplatin-based concurrent chemoradiotherapy could be considered as an alternative option, particularly where cisplatin is contraindicated.

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Author contributions

Conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: SMAH, MAB, UKS, MR, NKS, MJU. *Drafting the work or reviewing it critically for important intellectual content:* SMAH, MAB, UKS, MR, NKS, MJU. *Final approval of the version to be published: SMAH,* MAB, UKS, MR, NKS, MJU. *Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:* SMAH.

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

None

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