DOI: https://doi.org/10.53350/pjmhs20221612114

ORIGINAL ARTICLE

Concomitant Chemo-Radiotherapy with Oral Capecitabine in Locally Advanced Squamous Cell Carcinoma Cervix

AALIA BASHIR[1*], SANA MEHREEN[2], ANIS FATIMA[3], FAKHIRA JABEEN[4], AYESHA AHMAD[5]
[1]*Department of Oncology, Teaching Hospital, DGK-Pakistan*
[2]*Department of Oncology, Shaukat Khanum Hospital, Multan-Pakistan*
[3]*Department of Anatomy, LMDC, Lahore-Pakistan*
[4]*Department of Family Medicine, Rahim Hospital, Lahore-Pakistan*
[5]*Department of Oncology, GTTH, Lahore-Pakistan*
Correspondence to Dr. Aalia Bashir, Email: abia.khan333@gmail.com Tel:+92-333-6468684

ABSTRACT

Background: Cervical carcinoma is the fourth most common malignant neoplasm after carcinoma of the breast, lung, colorectal, endometrium and ovary.
Aim: To assess the all RECIST responses of concomitant chemo-radiotherapy with capecitabine in locally advanced squamous cell carcinoma cervix in a tertiary healthcare facility at Multan.
Methodology: It was a Descriptive case series Conducted at the Department of Clinical Oncology, Nishtar Hospital Multan. Patients (n=60) with locally advanced squamous cell carcinoma cervix received conventional radiation (Total Dose: 45Gy) with 825 mg/m^2 twice daily Capecitabine for five days a week for 6 weeks and followed by brachytherapy. Data was evaluated by using SPSS version 23. Post stratification Chi-square test was applied with P-value of 0.05 was considered as significant.
Results: Mean age of patient population was 39.5±6.8 (range: 31-52) years. Majority *i.e.* 30(50%) were between 30 to 40 years of age. The overall response rate was 88%, complete Response Rate was 80%, Partial Response rate was 8.3%, Stable Disease lasting ≥6 months was 5%, Progressive Disease was 6.7% in 60 patients at the end of treatment. Commonly observed performance status was ECOG 0 (n=57, 95.0%) while most of the patients had stage IIB at presentation (n= 35, 58.3%).
Practical Implication: Current project helped health providers to evaluate response rate to cervical carcinoma treatment to oral capeccitabine. With other chemo-drugs like Cisplatin, renal toxicity developed even with single low dose as elderly patients are more susceptible. Because renal toxicity of oral capecitabine was low as compared to cisplatin thus it was more effective than cisplatin. Due to low local data regarding oral capecitabine in cervical carcinoma as treatment option so planned present study.
Conclusion: It was concluded that patients of cervical carcinoma showed better response rate to concomitant chemo-radiation using Capecitabine with low renal toxicity.
Keywords: Cervical Cancer, Oral Capecitabine, Concurrent Chemo-Radiation and Brachytherapy.

INTRODUCTION

Cervical carcinoma is the fourth most common malignancy[1,2]. According to an estimate almost women (16/100,000/year) get cervical carcinoma with mortality occurs in 9/16 of its victims annually[3,4]. Globally, this disease has a high incidence (80%) especially in developing countries while squamous cell carcinoma is its most common (90%) type[5].

During concurrent chemotherapy, patient is given chemotherapy and radiation simultaneously. There happens an overlapping of various hematologic toxic effects due to chemotherapeutic agents thus more attention must be paid towards toxicity profile of chemotherapeutic agent. Various anti cancerous agents like Hydroxyurea, Cisplatin, 5-Fluorouracil, and Mitomycin-C have been used previously for its treatment[6].

Unfortunately, Recurrent and advanced cervical cancers are associated with high mortality especially among females who are unfit for surgery or radiation therapy.[3,4] According to various studies, Capecitabine has shown promising results as a radio sensitizer in squamous cell carcinoma of cervix.[7] Factors like broad clinical effectiveness and low toxicity profile among different malignancies advocates its use in cervical tumors treatment. Capecitabine is an oral 5-FU pro-drug; it is converted to 5-FU by enzyme thymidine phosphorylase (TP). Capecitabine and radiotherapy show preclinical synergy and clinical activity[6].

Dose-related and cumulative renal insufficiency is a major adverse effect related with Cisplatin. Literature review revealed that almost 36% patients developed renal toxicity even with a single dose of 50 mg/m^2.[8,9]. Current project helped health providers to evaluate response rate to cervical carcinoma treatment to oral capeccitabine. With other chemo-drugs like Cisplatin, renal toxicity developed even with single low dose as elderly patients are more susceptible. Because renal toxicity of oral capecitabine was low as compared to cisplatin thus it was more effective than cisplatin. Due to low local data regarding oral capecitabine in cervical carcinoma as treatment option so planned present study.

The objective of the study was to assess all RECIST responses of concomitant chemo-radiotherapy with capecitabine in locally advanced squamous cell carcinoma cervix in a tertiary healthcare facility at Multan.

Received on 14-07-2022
Accepted on 23-11-2022

METHODOLOGY

It was a descriptive case series conducted in the Department of Oncology Nishtar Hospital Multan including indoor and outdoor patients after approval from Ethical Review Board of hospital. Total 60 patients were enrolled in the study. Non-probability consecutive sampling was done. Female patients (aged 30-60 years) with biopsy proven Squamous Cell Carcinoma of cervix were included. Locally advanced squamous cell carcinoma cervix was determined by FIGO staging. (Stage IIB-IVA determined by detailed pelvic examination, ultrasound abdomen and pelvis and MRI pelvis). Exclusion Criteria were Resectable growth of Cervix on MRI pelvis, patients with metastatic disease and comorbidities *e.g.* Diabetes mellitus, ischemic heart disease and hypertension. Response rate was evaluated after eight weeks from start of study. Response Evaluation Criteria in Solid Tumors (RECIST) was used to assess following types of responses.

Complete history and physical examination and workup were performed before treatment including CBC, Serum Creatinine, LFTs, Abdominal USG and MRI pelvis. X-ray chest was performed to exclude lung metastasis. Capecitabine (500 mg) was given orally twice a day concomitant with radiation. Total of 45 Gy was delivered to the gross tumor volume defined by clinical examination and USG. Brachytherapy applications were given to deliver a total dose of 75Gy to the tumor.

Statistical analysis: Data will be entered and analyzed in SPSS version 23.0. Age was presented as mean and SD. Qualitative variables like FIGO stage and tumor response were presented as percentage and frequencies. Post stratification chi-square test was applied with P-value of 0.05 was considered as significant.

RESULTS

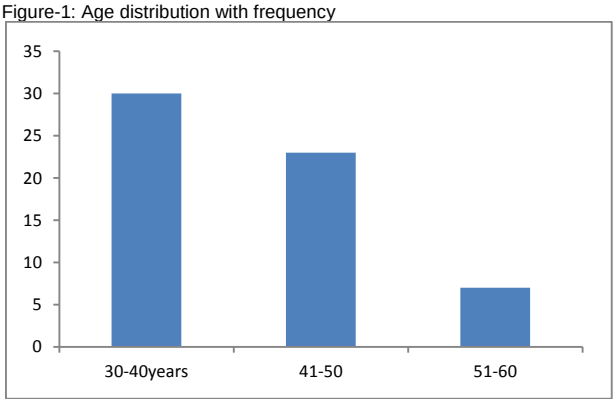
Mean age of patient population was 39.5±6.8 (range: 31-52) years. Majority *i.e.* 30(50%) were between 30 to 40 years of age (Table-1 and Figure-1). Commonly observed performance status was ECOG 0 57(95%) while most of the patients had stage IIB at presentation 35(58.3%) as shown in table-1.

Table-1: Baseline Parameters of enrolled population (n=60)

Characteristics	Frequency (%)
Age (Years)	
30-40	30 (50.0)
41-50	23 (38.3)
51-60	7 (11.7)
Age (Mean):	39.5±6.8
Performance Status	
ECOG0	57 (95.0)
ECOG1	3 (5.0)
Stage (FIGO)	
IIB	35 (58.3)
IIIA	1 (1.7)
IIIB	24 (40.0)

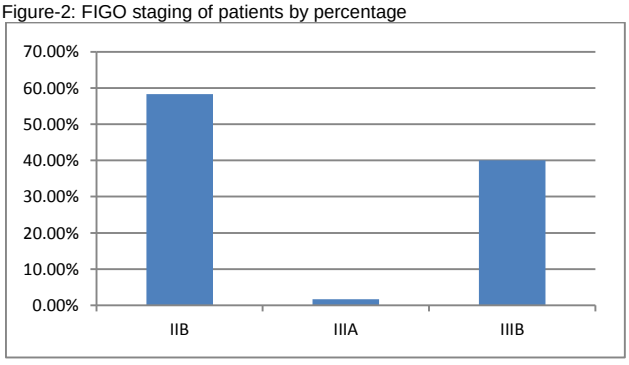
Figure-1 showed graphical presentation of age distribution with frequency.

Figure-1: Age distribution with frequency



Percentage distribution of patients on basis of FIGO staging was demonstrated by figure-2.

Figure-2: FIGO staging of patients by percentage



Stage IIB had complete response rate of 77.1%, it was 100% in IIIA disease and in IIIB complete response was observed to be 83.3% (Table-2). Partial response in IIB disease turned out to be 14.3% while PR was not observed in IIIA and IIIB (Table-2). Stable disease lasting ≥ 6 months in IIB disease was (2.9%), in IIIB disease it was (8.3%) while it was not recorded in IIIA disease (Table-2). Progressive disease was prevalent in IIIB i.e. 8.3% (Table-2).Treatment response was not affected by the disease stage (P = 0.579).

Table-2: Stage wise number and percentage of patients with different response rate

Stages	CR	PR	SD	PD
IIB (n=35)	27(77.1%)	5(14.3%)	1(2.9%)	2(5.7%)
IIIA (n=1)	1(100%)	0	0	0
IIIB (n=24)	20(83.3%)	0	2 (8.3%)	2(8.3%)
Overall	48(80%)	5(8.3%)	3 (5.0%)	4(6.7%)

Patient response rate to treatment with respect to age was tabulated in table-3 with significant p-value (0.007*).

Table-3: Stratification of response with regards to age groups (n=60)

Response	Age groups			P - value
	31-40	41-50	51-61	
Complete response	26	19	04	0.007*
Partial response	02	02	01	
Stable disease	00	00	2	
Progressive disease	02	03	00	

*Statistically significant

All sixty patients were evaluated for response assessment. Stratification of data was done with regard to performance status that showed insignificant p-value in table-4.

Table-4: Stratification of response with regards to performance status

Response	Performance status		P - value
	ECOG - 0	ECOG - 1	
CR	46	02	0.412
PR	04	01	
SD	02	00	
PD	05	00	

DISCUSSION

Previous studies reported that concomitant chemotherapy based on cisplatin showed better survival rate among patients in comparison to radiation treatment alone[10-12]. Thus, cisplatin-based chemo-radiation became standard treatment for cervical carcinoma patients. Chemo-radiation was significantly beneficial for local recurrence and the suggestion of a benefit for distant recurrence. However, the patients receiving concomitant chemoradiation had significantly higher acute hematological and gastrointestinal toxicity. Although, treatment-related deaths were uncommon but late effects of treatment were poorly documented thus hard to comment on late side effects of chemo-radiation[13,14].

One researcher gave 825 mg/m^2 twice daily radiation with capecitabine to the cervical carcinoma patients for five days a week for 6 weeks. As documented that oral capecitabine radio-sensitizes a wide variety of human cancer cell lines so this anti-cancerous agent was used.[15] His results showed 13% overall response rate.[16] Paradoxical to his findings, our results showed overall response rate of 88%. These results are concordant to other single agents such as cisplatin, paclitaxel, irinoticanor topotecan in same setting[17].

Capecitabine chemo radiotherapy is well tolerated treatment for locally advanced cervical cancer[18]. The simple and convenient administration schedule is an additional benefit to the patients as treatment can be administered on an outpatient basis.

The complete response rate in our study was 80% while 8.3% Partial response was observed. Similarly, one study reported that 91% complete response and improvement in quality of life with capecitabine chemoradiation[19]. The main difference between capecitabine chemo radiotherapy and other fluoropyrimidine based chemo radiotherapy regimens is synergism between capecitabine and radiotherapy resulting from TP up regulation. Based on this synergy we predict superior efficacy with capecitabine chemo-radiotherapy.

CONCLUSION

It was concluded that patients of cervical carcinoma showed better response rate to concomitant chemo-radiation using Capecitabine

with low renal toxicity. Thus high response to treatment advocates Capecitabine radio-sensitive property.

Author's contribution: AB&SM: Overall supervision, write up and literature review., **AF&FJ:** Statistics application, analysis literature review, help in write up, **AA:** Literature review help in write-up.

Limitation of study: Treatment planning system facility is not available at our Institute which is mandatory for optimization of dose distribution in the treatment volume. We use 2-DRT technique, with which we cannot exceed 60 Gy radiation dose, a minimum recommended dose for cervical cancers but cannot completely sterilize the tumor cells. Although our study showed modest response rate in cervical cancer, to see whether this response rate is translated into overall survival benefit or not was not assessed. The toxicity related to our treatment protocol seems to be quite low and may even have increased overall survival. A longer follow up might be of help in answering this important issue as response and toxicity occur up to months after completion of treatment.

Conflict of interest: Nil

Funding: None

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66:7–30.
2. Maltese G, Lepori S, Sabatucci I, et al. Int J Gynecol Cancer 2019;29:272–276.
3. S. Movva, L. Rodriguez, H. Arias-Pulido, and C. Verschraegen, "Novel chemotherapy approaches for cervical cancer," Cancer, vol. 115, no. 14, pp. 3166–3180, 2009.
4. Montzois G, Soultati A, Pectasides D, Dimopoulos MA, Papadimitriou CA. Novel Approaches for Concurrent Irradiation in Locally Advanced Cervical Cancer: Platinum Combinations, Non-Platinum-Containing Regimens, and Molecular Targeted Agents. Obstetrics and Gynecology International Volume 2013, Article ID 536765, 8 pages http://dx.doi.org/10.1155/2013/536765
5. Carlos A Perez,BrainD. Kavanagh, gynecologic tumors, uterine cervix. Principles and practice of Radiation oncology; Lippin Cott Wiliam and Wilkins,2012;1800-1915.
6. Domingo E, Lorvidhaya V, Reyes RDL, *et al.* Capecitabine-Based Chemoradiotherapy with Adjuvant Capecitabine for Locally Advanced Squamous Carcinoma of the Uterine Cervix: Phase II Results. The Oncologist 2009;14:828 – 834. doi: 10.1634/theoncologist.2009-0041.
7. Donnelly ED, Refaat T, Gentile M, Herskovic A, Boyle J, Helenowski I, et al. Evaluation of Outcomes in Patients With Carcinoma of the Cervix Treated With Concurrent Radiation and Cisplatin Versus Cisplatin/5-FU Compared With Radiation Alone. Am J Clin Oncol 2015; 38:437–441.
8. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev. 2010;1:CD008285.
9. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2009. 2011. Available at: http:// www.seer.cancer.gov/.
10. Hamedi B, Hooshmand S, Mosalaie A, Robati M, Momtahan M, Farhadi P, et al. The effect of extrafascial hysterectomy after completion of external beam radiotherapy for treatment of locally advanced stages (IIB-III) of cervical cancer:Iran Red Cres Med J.2013;15(12).
11. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Sugg CL, et al.:Cisplatin radiation and adjuvant hysterectomy. J Clin Oncor 2011;11:999s-15s.
12. Rose PG, Combined modality therapy of locally advanced cervical cancer. J Clin Oncor 2013;21:211s-17s.
13. Choo YC, Choy TK, Wong LC, Ma HK, Potentiation of radiotherapy by cis-dichlorodiammineplatinium in advanced cervical carcinoma; Gynecol Oncol.1986 Jan;23(1) 94-1.
14. .Mierzwa LM, Nyati KM, Morgan AM, Lawrenence ST, Maruyama Y, Ayala R, et al. Resent Advances in combined Modality therapy. The Oncologist 2010;15:372-381.
15. Sawada N, Ishikawa T, Sekiguchi F. **X** ray irradiation induces thymidine Phosphorylase and enhances the efficacy of Capecitabine (Xeloda) in human cancer Xenografts. Clin Cancer Res2009;5:2948-53.
16. Lorvidhaya V, Phromratanapongs P ,Chitapanarux I et al.A phase II study of Capecitabine who have failed first-line treatment in locally advanced or metastatic cervix cancer [abstract 174]. Eur J Cancer suppl 2013;1:3991.
17. Long HJ 3rd.Management of metastatic cervical cancer: Review of literature. Clin Oncol 2012; 25:2966-2974.
18. Rose PG, Bundy BN, Watkins EB et al. Conconcurrent cisplatin based chemotherapy and radiotherapy for locally advanced cervical cancer. N Engl J Med 1999; 340:1144-1153.
19. Padilla P, Torricellas L, Ayala R *et al.* Capecitabine (X) chemoradiation as first line treatment in patients with stage IIB-IIIB squamous cel carcinoma cervix. a Mexican radio-oncology study group trial [abstracr 927]. Eur J Cancer Suppl 2013;2:26.