RESPONSE EVALUATION OF NEO ADJUVANT CHEMOTHERAPY WITH CISPLATIN AND 5-FLUROURACIL IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF CERVIX

MUHAMMAD TAHIR, MUHAMMAD ABBAS KHOKHAR, MAHAM TASEER, SAMINA QAMAR
[1]Department of Oncology, Allied Hospital Faisalabad. [2]Department of Oncology, King Edward Medical University Lahore. [3]Department of Oncology, King Edward Medical University, Lahore. Department of Pathology King Edward Medical University Lahore. Correspondence: khokhars44@gmail.com

ABSTRACT

Objective: To assess the frequency of different responses of neoadjuvant therapy with cisplatin and 5-flourouracil in patients presenting with locally advanced squamous cell carcinoma of cervix.

Patients and Methods: This was a descriptive case series study conducted at Department of Oncology, Jinnah Hospital, Lahore from 10-07-2015 and completed on 9-01-2016. One hundred and fifty patients were included. Selected patients received chemotherapy with Cisplatin 75mg/m^2 on day 1 and 5-flurouracil 750 mg/m^2/day continuous infusion from day1 to day5, 3 weekly for a total of 2 cycles. Response assessment was done after completion of 2 cycles of chemotherapy and it was documented as either complete response (CR) or Partial response (PR) or Stable Disease (SD) or Progressive Disease (PD) according to Standard Method of "Response Evaluation Criteria in Solid Tumors(RECIST 1.1)" with CT scan.

Results: Mean age of study population was 48.19±6.23 year. Majority (49 patient or 32.7%) had stage IIIb disease, 21(14 %) patients had stage IIB disease, 33 (22%) had stage IIIa and 47 (31.3%) had stage IVA disease at baseline. Fifty patients (33.3%) had lymph node involvement and100 patients (66.7%) had no lymph nodal involvement. 116 (77.3%) patients had ECOG performance status of 1 and remaining had performance status of 2.Partial response was seen in 15 (12.7%) with stage IIb patients, 24(20.3%) with stage IIIa, 39 (33.1%) with stage IIIb patients and 40 (33.9%) with stage IVa patients. Stable disease was seen in 4(16.7%) with IIb, 6(25%) with IIIa, 8(33.3%) with IIIb and 6(25%) with IVa patients. Complete response was seen in 2(28.6%) with IIb,3(42.9%) with IIIa, and 1(14.3%) with IIIb and IVa patients each. Progressive disease was seen in only one patient with stage IIIb. Response rates in stage IIIB and IVa patients were better than the stage IIb and IIIa patients but it was not statistically significant.

Conclusion: Neo-adjuvant chemotherapy has fair response rates in locally advanced squamous cell carcinoma of cervix. In resource constraint countries like Pakistan where due to lack of treatment facilities like radiotherapy and skilled oncological surgeons many patients miss the chance of cure due to long waiting times, Neo-adjuvant chemotherapy can be used as a bridge therapy in patients who are waiting for definitive treatment options.

Key words: Squamous cell carcinoma, cervical cancer, Locally advanced cancer, Neo-adjuvant Chemotherapy

INTRODUCTION

Cervical cancer is the most common gynecologic cancer in women all over the world. An estimated 12,360 new cases of carcinoma of the uterine cervix (i.e. cervical cancer) were diagnosed in the United States in 2014, and 4020 people died of the disease.[1] Although Cervical cancer rates are decreasing among women in the United States, Incidence still remains high among Hispanic/Latino, Black, and Asian women.[2-5] The global yearly incidence of cervical cancer in 2012 was 528,000; the annual death rate was 266,000.[6] It is the fourth most common cancer in women worldwide, with 85% of cases occurring in developing countries, where cervical cancer is a leading cause of cancer death in women [7-9]. In Punjab cancer registry report of 2014 , published in March 2015, it was the 2nd most commonly reported cancer in women and the third most common cause of cancer related deaths in women following breast, lip and oral cavity cancers.

Persistent human papillomavirus (HPV) infection is the most important causative factor in the development of cervical cancer[10,11]. Prevalence of chronic HPV is approximately 10% to 20% in countries with high incidence of cervical cancer whereas prevalence of HPV in low-incidence countries is around 5% to 10%.[7] Immunization against HPV prevents

infection only with the some specific types of HPV and thus is expected to prevent specific HPV cancer in women.[12-16] Other epidemiological risk factors associated with cervical cancer are smoking, parity, oral contraceptive, early age at first coitus, multiple sexual partners, history of sexually transmitted disease, autoimmune diseases, and chronic immunosuppression.[17,18] Squamous cell carcinomas (SCC) comprise approximately 80% of all cervical cancers and adenocarcinoma makes almost 20% of total cancers.[18] In developed countries, the decline in incidence and mortality of SCC of cervix is presumed to be the result of effective screening, although racial, ethnic, and geographic disparities still exist.[2,3,19,20] On the contrary, Adenocarcinoma of the cervix has increased over the past 3 decades, probably because cervical cytological screening methods are less effective for adenocarcinoma.[21-24] Screening methods using HPV testing on papaniculaou smears may increase detection of adenocarcinoma. Vaccination with HPV vaccines may also decrease the incidence of both SCCand Adenocarcinoma.[23,25]

The primary treatment of early-degree cervical most cancers is either surgery or radiotherapy (RT). Smaller lesions and early-level disease, such as level IA, IB1, and decided on IIA1 are dealt with surgical procedure.[26] Combination of chemo-radiation is generally the treatment of choice for stages IB2 to IVA.[27,28] Chemoradiation can also be used for patients who cannot undergo hysterectomy. Adenocarcinomas are treated in a similar manner to squamous cell carcinomas, although few studies have assessed treatment modalities.[29-31]

There is a trend now in favour of neoadjuvant chemotherapy (NACT).[32,33] There is limited data on neoadjuvant chemotherapy but in one study reported by PubMed[34], sixty-seven patients received neoadjuvant chemotherapy. Clinical responses to neoadjuvant chemotherapy observed in 61 patients(91%), including six (8.96%) with complete and 55 (82.0%) with partial response; five women(7.46%) showed stable disease and one progressed(1.49%).In many hospitals of our country, there is a delay of 3 months on an average to get radiotherapy started after presentation due to overburden of patients. During this period, there is a high likelihood of disease progression making the patients incurable. Furthermore systemic chemotherapy decreases micrometastases which are not targeted by local radiotherapy. So keeping in view the current trend in favour of NACT in study trials, the risk of progression of stage while waiting to get radiotherapy started in JHL and benefits of NACT on micrometastases, this study was designed to observe the response of NACT cisplatin and 5-flourouracil in patients presenting with locally advanced squamous cell carcinoma of cervix.

MATERIAL AND METHODS

It was a descriptive case series study carried out at Department of Oncology, Jinnah Hospital, Lahore from 10-7-2015 and completed on 09-01-2016 comprised 150 patients. Patients age 20-70 years, female patients with histopathologically proven squamous cell carcinoma of cervix during last one year, stage IIB- IVA and ECOG performance status<3 were included. Patients who have received any treatment (chemotherapy, radiotherapy) prior to presentation, adenocarcinoma of cervix proven by histopathology, abnormal cardiac function assessed with ECG, renal function with serum creatinine (>1.5mg/dl) and liver function tests with serum transaminases level>100 u/l and starting radiotherapy while on NACT were excluded. Selected patients will receive chemotherapy with cisplatin 75 mg/m^2 on day 1 and 5-flourouracil 750 mg/m^2 on days 1-5 of 21 day cycle for a total of 2 cycles. Response in terms of either CR,PR, SD or PD will be evaluated as per RECIST criteria edition 1.1 after 3 weeks of last chemotherapy with CT scan. Data was entered in SPSS-20 and analyzed.

RESULTS

Mean age of our patient population was 48.19±6.23 years and median age was 47 years. Youngest patient was 32 years old and oldest was 66 years old. Amongst them 54 (36.0%) patients were between 32 to 45 years of age and 96 (64.0%) were aged between 46 to 66 years. Out of 150 patients, majority (49 patients or 32.7%) had stage IIIb disease, 21(14 %) patients had stage IIB disease, 33 (22%) had stage IIIa and 47(31.3)% had stage IVA disease at baseline. 50 patients (33.3%) had lymph node involvement and 100 patients (66.7%) had no lymph nodal involvement. 116(77.3%) patients had ECOG performance status of 1 and remaining had 2. Response to neo-adjuvant chemotherapy was assessed after 2nd cycle of chemotherapy and was documented either as complete response, partial response, stable disease or progressive disease. Partial response was observed in 118 (78.7%) of patient. As compared to target response rate of stable disease of 7.46%, stable disease was observed in 24 (16 %) patients, this result was statistically not significant with. 7 patients (4.7%) showed complete response, one patient (0.7%) showed progressive disease on assessment after the 2nd cycle(Table 1).

Partial response was seen in 15(12.7%) with stage IIb patients, 24(20.3%) with stage IIIa,39(33.1%) with

stage IIIb patients and 40(33.9%) with stage IVa patients. Stable disease was seen in 4(16.7%) with IIb, 6(25%) with IIIa, 8(33.3%) with IIIb and 6(25%) with IVa patients. Complete response was seen in 2(28.6%) with IIb,3(42.9%) with IIIa, and 1(14.3%) with IIIb and IVa patients each. Progressive disease was seen in only one patient with stage IIIb. Response rates in stage IIIB and Iva patients were better than the stage IIb and IIIa patients but it was not statistically significant (Table2)

Partial response rate was seen in 93 (78.8%) of patients with ECOG1 and 25(21.2%) of patients with ECOG2.Stable disease was seen in 19(79.2%) of patients with ECOG1 and 5(20.8%) 0f patients with ECOG 2.Complete response rate was seen in 4(57.1%) of patients with ECOG 1 and 3(42.9%) of patients with ECOG2.Progressive disease was seen in only one patient with ECOG 2.Differences in these results were also statistically not significant (Table 3).

Table 1: Demographic information of the patients

Variable	**No.**	**%**
Age (years)		
32 – 45	54	36.0
46 – 66	96	64.0
TNM Stage		
IIb	21	14.0
IIIa	33	22.0
IIIb	49	32.7
Iva	47	31.3
Nodal Status		
Present	50	33.3
Absent	100	66.7
ECOG Performance		
Restricted in physically strenuous activity but ambulatory and able to carry out light work (ECOG1)	116	77.3
Ambulatory and capable of all self-care. Up and above >50% of working hours (ECOG2)	34	22.7
Responses to neo-adjuvant chemotherapy		
Partial response	118	78.7
Stable disease	24	16.0
Complete response	7	4.7
Progressive disease	1	0.7

Table 2: Comparison of response rates according to TNM stage

Response	**TNM Stage**				**Total**
	IIb	IIIa	IIIb	IVa	
Partial response	15 (12.7%)	24 (20.3%)	39 (33.1%)	40 (33.9%)	118 (100%)
Stable disease	4 (16.7%)	6 (25%)	8 (33.3%)	6 (25%)	24 (100%)
Complete response	2 (28.6%)	3 (42.9%)	1 (14.3%)	1 (14.3%)	7 (100%)
Progressive disease	-	-	1 (100%)	-	1 (100%)

$\chi^2 = 6.952$ P = 0.642

Table 3: Comparison of response rates according to ECOG performance status

Response	**ECOG performance status**		**Total**
	ECOG1	ECOG2	
Partial response	93 (78.8%)	25 (21.2%	118 (100%)
Stable disease	19 (79.2%)	5 (20.8%)	24 (100%)
Complete response	4 (57.1%)	3 (42.9%)	7 (100%)
Progressive disease	-	1 (100%)	1 (100%)

$\chi^2 = 5.233$ P = 0.155

DISCUSSION

Use of neo-adjuvant chemotherapy is theoretical supposed to have some advantages like possible improvement of baseline symptoms, the down staging of tumor, and clearing of micro metastases in regional lymph nodes and distant organs. Neo-adjuvant chemotherapy with cisplatin and 5-flurouracil has also reported to have induced immunological reaction in the cancer micro environment resulting in better outcomes.

The mean age of study population was 48.19±6.23 years which was lower than the internationally reported age of 67 years, which may be due to overall lower life expectancy in Pakistan which is only 65 years as compare to 78 to 80 years in developed countries. The overall partial response rate of 78.7% is somewhat lower than reported partial response rates of 82%[34]. This could have been due to less number of chemotherapy cycle (only 2) as compare to otherstudies[32,33] where 3 or more cycles were given of these two drugs or a third drug was also added.

In this study,7 patients (4.7%) showed complete response which is lower than reported complete response rates of 8.96%. which is comparable to the results of previous studies done in recent times, with reported CR rates of 0%–10%[32-34]. No such data is available from Pakistan for comparison. Although investigators were initially encouraged by high response rates of untreated cervical cancer to multiple-agent, cisplatin-containing chemotherapy regimens, these results have not translated to a clear advantage when neoadjuvant chemotherapy is given before radiotherapy. Of seven phase 3 trials of this approach, five[35-37] demonstrated no benefit from neoadjuvant therapy and two[38]demonstrated a significantly better survival rate with radiotherapy alone.

Subset analysis in this study showed partial response in 15(12.7%) of stage IIb patients, 24(20.3%) of stage IIIa,39(33.1%) of stage IIIb patients and 40(33.9%) of stage IVa patients. Stable disease was seen in 4(16.7%) of IIb, 6(25%) of IIIa, 8(33.3%) of IIIb and 6(25%) of IVa patients. Complete response was seen in 2(28.6%) of IIb,3(42.9%) of IIIa, and 1(14.3%) of IIIb and IVa patients each. Progressive disease was seen in only one patient of stage IIIb. Response rates in stage IIIB and IVa patients were better than the stage IIb and IIIa patients but it was not statistically significant.

Similar results were obtained in patients between performance status 1 and 2 patients, Partial response rate was seen in 93 (78.8%) of patients with ECOG1 and 25(21.2%) of patients with ECOG2.Stable disease was seen in 19(79.2%) of patients with ECOG1 and 5(20.8%) 0f patients with ECOG 2.Complete response rate was seen in 4(57.1%) of patients with ECOG 1 and 3(42.9%) of patients with ECOG2.Progressive disease was seen in only one patient with ECOG 2.Differences in these results were also statistically not significant.

CONCLUSION

With the results of this study we can conclude that neo-adjuvant chemotherapy has fair response rates in patients presenting with locally advanced squamous cell carcinoma of cervix. It is a good option to use in resource constraint countries like Pakistan where due to lack of treatment facilities like radiotherapy and delay of time to get radiotherapy started due to over burdened radiotherapy departments. In this study we also observed better response rates in stage IIIb and Iva patients as compare to stage IIb and IIIa patients, although this difference was not statistically significant.

REFERENCES

1. R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin2014;64:9-29.
2. Barnholtz-Sloan J, Patel N, Rollison D, et al. Incidence trends of invasive cervical cancer in the United States by combined race and ethnicity. Cancer Causes Control 2009;20:1129-38.
3. Wang SS, Carreon JD, Gomez SL, Devesa SS. Cervical cancer incidence among 6 asian ethnic groups in the United States, 1996 through 2004. Cancer 2010;116:949-56.
4. Howe HL, Wu X, Ries LAG, et al. Annual report to the nation on the status of cancer, 1975-2003, featuring cancer among U.S.Hispanic/Latino populations. Cancer 2006;107:1711-42.
5. Sherman ME, Wang SS, Carreon J, Devesa SS. Mortality trends for cervical squamous and adenocarcinoma in the United States. Relationto incidence and survival. Cancer 2005;103:1258-64.
6. International Agency for Research on Cancer. Cervical CancerEstimated Incidence,Mortality and Prevalence Worldwide in 2012.World Health Organization; 2012.
7. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002.CA Cancer J Clin 2005;55:74-108.
8. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence,mortality, and prevalence across five continents: defining priorities toreduce cancer disparities in different geographic regions of the world. JClinOncol2006;24:2137-50
9. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CACancer J Clin 2011;61:69-90.

10. Kjaer SK, Frederiksen K, Munk C, Iftner T. Long-term absolute riskof cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. J Natl Cancer Inst2010;102:1478-88.
11. Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study ofhuman papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. J Natl Cancer Inst 2010;102:315-24.
12. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271-8.
13. Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007;369:1861-8.
14. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-27.
15. Arbyn M, Dillner J. Review of current knowledge on HPV vaccination: an appendix to the European Guidelines for Quality Assurance in Cervical Cancer Screening. J Clin Virol 2007;38:189-97.
16. Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. CMAJ 2007;177:469-479.
17. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer 2007;120:885-891.
18. Dugue PA, Rebolj M, Garred P, Lynge E. Immunosuppression and risk of cervical cancer. Expert Rev Anticancer Ther 2013;13:29-42.
19. Bray F, Loos AH, McCarron P, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. Cancer Epidemiol Biomarkers Prev 2005;14:677-686
20. Watson M, Saraiya M, Benard V, et al. Burden of cervical cancer in the United States, 1998-2003. Cancer 2008;113:2855-2864.
21. Bray F, Carstensen B, Moller H, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 2005;14:2191-2199.
22. Wang SS, Sherman ME, Hildesheim A, et al. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. Cancer 2004;100:1035-1044
23. Castellsague X, Diaz M, de Sanjose S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst 2006;98:303-315.
24. Sasieni P, Castanon A, Cuzick J. Screening and adenocarcinoma of the cervix. Int J Cancer 2009;125:525-529.
25. Dahlstrom LA, Ylitalo N, Sundstrom K, et al. Prospective study of human papillomavirus and risk of cervical adenocarcinoma. Int J Cancer 2010;127:1923-1930.
26. ACOG practice bulletin. Diagnosis and treatment of cervicalcarcinomas. Number 35, May 2002. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 2002;78:79-91.
27. Gaffney DK, Erickson-Wittmann BA, Jhingran A, et al. ACR Appropriateness Criteria (R) on Advanced Cervical Cancer Expert Panel on Radiation Oncology-Gynecology. Int J Radiat Oncol Biol Phys 2011;81:609-14.
28. Monk BJ, Tewari KS, Koh W-J. Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. J Clin Oncol 2007;25:2952-65.
29. Gien LT, Beauchemin MC, Thomas G. Adenocarcinoma: a unique cervical cancer. Gynecol Oncol 2010;116:140-146.
30. Baalbergen A, Veenstra Y, Stalpers LL, Ansink AC. Primary surgery versus primary radiation therapy with or without chemotherapy for early adenocarcinoma of the uterine cervix. Cochrane Database Syst Rev 2010:CD006248.
31. Park JY, Kim DY, Kim JH, et al. Outcomes after radical hysterectomy in patients with early-stage adenocarcinoma of uterine cervix. Br J Cancer 2010;102:1692 –1698.
32. Ye Q, Yuan Hx,Chen HL. Responsiveness of neo adjuvant chemotherapy before surgery predicts favourable prognosis for cervical cancer patients: a meta analysis. J Cancer Res Clin Oncol 2013;139:1887-98.
33. Landoni F , Sartori E, Maggino T.Is there a role for postoperative treatment in patients with stage

Ib2-IIb cervical cancer treated with neo adjuvant chemotherapy and radical surgery ?An Italian multicentre retrospective study. GynecolOncol

34 .Zhongua Zhong Liu Za Zhi. Neo adjuvant chemotherapy for locally advanced uterine cervical cancer. 2014;132:611-617.

35. Chauvergne J, Rohart J, Héron JF, et al. Randomized trial of initial chemotherapy in 151 locally advanced carcinoma of the cervix (T2b-N1, T3b, MO). Bull Cancer 1990;77:1007–1024.

36. Leborgne F, Leborgne JH, Doldán R, et al. Induction chemotherapy and radiotherapy of advanced cancer of the cervix: a pilot study and phase III randomized trial. Int J Radiat Oncol BiolPhys 1997;37:343–350.

37. Sundfør K, Trope CG, Hogberg T, et al. Radiotherapy and neoadjuvant chemotherapy for cervical carcinoma. A randomized multicenter study of sequential cisplatin and 5-fluorouracil and radiotherapy in advanced cervical carcinoma stage 3B and 4A. Cancer 1996;77:2371–8.

35. American Cancer Society. Cancer Facts and Figures 2014. Atlanta, GA: American Cancer Society; 2014.

36. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated CancerIncidence, Mortality and Prevalence Worldwide 2012

37. Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. CA Cancer J Clin1995;45:8–30.

38. Bosch FX, de Sanjose S. Chapter 1: Human papillomavirus and cervical cancerburden and assessment of causality .J Natl Cancer Inst Monogr 2003;31:3–13.