ORIGINAL ARTICLE

Concurrent Cisplatin-Based Chemoradiation in Squamous Cell Carcinoma of Cervix

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Abstract

Objective: To evaluate the efficacy of cisplatin-based concurrent chemoradiation in squamous cell carcinoma of cervix and the frequency of acute toxicity.

Study Design: Case series.

Place and Duration of Study: Department of Clinical Oncology, Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi, from September 2010 to September 2011.

Methodology: Eighty patients with histologically proven squamous cell carcinoma of cervix were included. Patients were treated with concurrent chemoradiation. External beam radiation was delivered with 50 Gy whole pelvis along with 40 mg/m^2 weekly cisplatin followed by brachytherapy three insertions of 6.5 Gy each, one week apart. Response to treatment was assessed using response evaluation criteria in solid tumours (RECIST) criteria at 4 weeks after treatment. Acute toxicity of chemoradiation was assessed using common toxicity criteria.

Results: Out of the 80 patients, 8 patients were lost to follow-up. Remaining 72 patients aged 28 - 65 years with mean age of 48.03 ±8.9 years. Forty-eight patients (66%) were in stage II-B, 5 (7%) were in stage III-A, 7 (10%) were in stage III-B, and 12 (17%) were in stage IV-A. Overall response to treatment was 92%, in which 39 (54%) had complete response, and 27 (38%) had partial response while 6 (8%) show progressive disease. About 70% patients had diarrhea, 61.2% patients developed vomiting, 45.8% patients had dermatitis, 43% patients had vaginal mucositis, 40.3% had anemia, 13.9% patients had neutropenia, 27.8% patients had dysuria, and 22.2% patients had proctitis.

Conclusion: Cisplatin-based concurrent chemoradiation is an effective treatment in locally advanced stage of cervical cancer with manageable toxicity.

Key Words: *Cervix. Cisplatin. Radiotherapy. Brachytherapy. Squamous cell carcinoma.*

INTRODUCTION

Cancer of cervix uteri is a major health problem worldwide. It is the second most common cause of cancer related mortality among women globally causing approximately 234,000 deaths annually in developing countries and killing 40,000 in developed countries.[1]

According to the statistics at Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), cervical cancer ranks the 3rd most common cancer in females accounting for 5.5%, showing peak incidence in age group of 40 - 60 years.[2] Treatment for early stage IA-IIA cervical cancers is surgery or radiotherapy. But for more advanced stages beyond II-B, chemoradiation is the standard of care.[3]

In 1999, five randomized clinical trials reported significant improvement in disease-free and overall survival for advanced cervical cancer in patients through concurrent administration of cisplatin-based chemotherapy with radiation therapy.[4-8] The results have shown a 30 - 50% decrease in the risk of death compared to radiation alone. Since then, the National Cancer Institute of America issued a strong recommendation for inclusion of cisplatin-based chemotherapy with concurrent radiotherapy in treatment of cervical cancer.[9]

Review of local literature revealed that concurrent chemoradiation is being done at King Edward Medical College, Lahore[10] and Nuclear Medicine Oncology and Radiotherapy Institute, Islamabad.[11] At Lahore, chemoradiation showed overall response in 89% of the patients and toxicity of chemoradiation were manageable.[10] Most common toxicity was gastrointestinal symptoms like nausea and vomiting (52%) and diarrhea (15%). Others were genitourinary like dysuria and vaginitis.[10]

As most of the cancers presented in locally advanced stage, chemotherapy along with concurrent radiation would produce good response as it acts as a radiosensitiser and decreases the bulk of disease by its cytotoxic effect. Result of the study would enable to improve practice with manageable toxicities and in future, it would become our institutional protocol.

The objective of this study was to evaluate the response of cisplatin-based chemoradiation in cervical cancer at KIRAN, Karachi.

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METHODOLOGY

The study was carried out at Karachi Institute of Radiotherapy and Nuclear Medicine from September 2010 to September 2011. It was a case series. Patients were enrolled in the study through radiotherapy OPD of the Institute. The inclusion criteria was patients with histologically proven squamous cell carcinoma of cervix in stage II-B-IVA with normal blood count, hepatic and renal function. The exclusion criteria was patients above 70 years, with ECOG 3 and above and metastatic disease. Informed written consent was taken and duly signed by the patients. Ethical Review Committee of the institute approved the study.

Staging was based on examination under anaesthesia using FIGO staging and MRI pelvis with contrast. Stage IV-A patients were confirmed by rectal examination and cystoscopy. Radiation was given via parallel opposed anterioposterior and lateral fields using linear accelerator (15 mv photons). External beam radiotherapy was given with a dose of 1.8 Gy/day, 5 days a week up to 50.4 Gy in 28 fractions. Injection cisplatin 40 mg/m^2 was given weekly during radiation. Patients were examined weekly as well as at the end of treatment for side effects during radiation.

After completion of external beam radiotherapy, patients were planned for brachytherapy. After aseptic measures under local anaesthesia and intravenous sedation, fletcher suit with long tandem was placed in uterus and ovoids in vagina. Dose to the rectum and bladder were kept with respect to tolerance dose. Dose was specified at point A is taken as 2 cm above cervical os and 2 cm lateral to uterine axis. Treatment was carried out on the remote afterload brachytherapy unit. Three insertions of HDR brachytherapy were done with Irridium-192, one week apart at 6.5 Gy per week. Radiation safety measures were carried out during treatment.

Treatment response was assessed at 4 weeks by clinical examination and confirmed radiologically by MRI scan using RECIST. Acute toxicity of the chemoradiation was assessed using common toxicity criteria.

After collection of data, it was analyzed using Statistical Package for Social Science (SPSS) version 17. Categorical data, like stage of disease, response rate, and grade of toxicity was expressed in frequency and percentages. For age, mean ± standard deviation was calculated. Stratification was done with regards to the stage of disease to see the effect of these on outcome.

RESULTS

A total of 80 patients with squamous cell carcinoma of cervix were included in this study. Eight patients were lost to follow-up. Remaining 72 patients were in the age group of 28 - 65 years with the mean age of 48.03 ±8.9 years.

According to stage of the disease, 48 (66%) were in stage II-B, 5 (7%) were in stage III-A, 7 (10%) were in stage III-B while 12/72 (17%) were in stage IV.

Overall response to treatment was 92%, out of which 39 (54%) had complete response and 27 (38%) had partial response (Figure 1). Treatment response with respect to stage shown in Table I.

Regarding side effects of treatment, 44 (61.2%) patients had vomiting, 50 (69.4%) had diarrhea, 33 (45.8%) had dermatitis, 31 (43%) had vaginal mucositis, 29 (40.3%) had anemia, 10 (13.9%) patients had neutropenia, 20 (27.8%) had dysuria, and 16 (22.2%) had proctitis. Severity of grades of toxicity is shown in Table II.

DISCUSSION

Since the 1980s, many phase I-II studies have established that treatment with cisplatin, 5-fluorouracil and mitomycin can safely be combined with pelvic radiation in cervical cancer.[12,13] Since the rate of complete response expected with the use of radiation therapy alone is high, whether there is any incremental

Table I: Treatment response with respect to stage.

Treatment response	Number	Stage II-B	Stage III-A	Stage III-B	Stage IV-A
Complete response	39	36 (92.3%)	0	2 (5.1%)	1 (2.6%)
Partial response	27	11 (40.7%)	5 (18.5%)	5 (18.5%)	6 (22.2%)
Progressive disease	6	1 (16.7%)	0	0	5 (83.3%)

Table II: Frequency of grades of acute toxicity profile.

Toxicity	Severity of Grades				
	G0	G1	G2	G3	G4
Vomiting	28 (38.9%)	26 (36.1%)	17 (23.6%)	1 (1.4%)	0 (0%)
Diarrhea	12 (16.7%)	27 (37.5%)	19 (26.4 %)	4 (5.6%)	0 (0%)
Dermatitis	39 (54.2%)	21 (29.2%)	6 (8.3 %)	5 (7.0%)	1 (1.4%)
Vaginal mucositis	41 (57.0 %)	20 (27.8%)	5 (7.0%)	5 (7.0%)	1 (1.4%)
Anemia	43 (60.0%)	23 (32%)	6 (8.3%)	0 (0%)	0 (0%)
Neutropenia	62 (86.1%)	8 (11.1%)	2 (2.8%)	0 (0%)	0 (0%)
Dysuria	52 (72.2 %)	17 (23.6%)	2 (2.8%)	1 (1.4%)	0 (0%)
Proctitis	56 (77.8%)	14 (19.4%)	2 (2.8%)	0 (0%)	0 (0%)

NCI: Common Toxicity Criteria

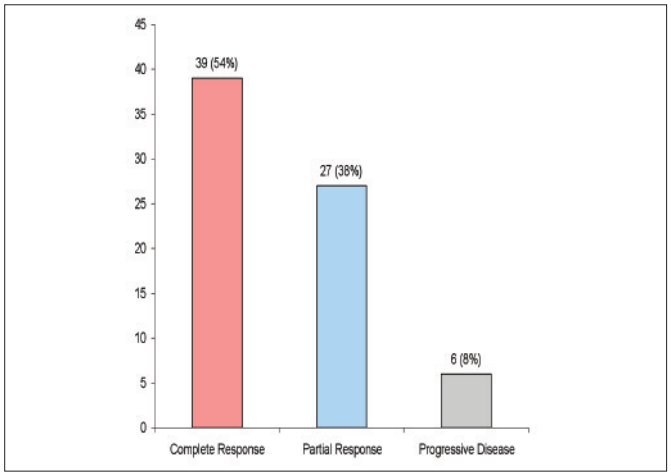

Figure 1: Frequency of response of chemoradiation in patients with carcinoma of cervix.

benefit from the added chemotherapy could not be assessed in phase II studies. Answers to these questions came from phase III trials of this strategy. In 1999, five randomized clinical trials reported significant improvement in disease-free and overall survival for advanced cervical cancer in patients through concurrent administration of cisplatin-based chemotherapy with radiation therapy.[4-8]

Based on the results of these trials, the National Cancer Institute in 1999 issued a clinical announcement that strong consideration should be given to incorporation of cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer.[14] Since then, concurrent chemoradiation has become the standard of care in locally advanced cervical cancers.

Chemotherapy may act synergistically with radiotherapy by inhibiting the repair of radiation induced damage, promoting the synchronization of cells in the 'S' phase of the cell cycle and reducing the fraction of hypoxic cells that are resistant to radiation.

The ability of radiotherapy to cure locally advanced cervical cancer is limited by the size of the tumor. Therefore, to improve the results of treatment in advanced stage disease, chemotherapeutic agents also have been used for the last 2 - 3 decades as neoadjuvant, concurrent chemoradiation and adjuvant therapy. But only concurrent chemoradiation with cisplatin alone or in combination with other agents like 5-fluorouracil have recently been proven to give better response rates, disease-free survival, and overall survival in carcinoma cervix.[15]

This study was conducted to find out the role of chemoradiation in advanced cervical cancer. Cisplatin was chosen as it has good radiosensitizing power resulting in higher progression-free survival as compared to others.[16]

In this study, the overall response to treatment was 92%, out of which 54% had complete response, 38% had partial response while 8% had progressive disease. Progression of disease was seen in those patients who had undue gap in in-between radiation treatment, triggering accelerated repopulation of surviving clonogens and cross-resistance to further radiotherapy. Though it was intended to start brachytherapy without delay but, there were problems beyond control such as patient load, and public holidays etc.

Analysis of treatment response, according to stage, showed that there was an indirect correlation between stage of the disease and complete response. As stage increases from stage II-B to IV-A, rate of complete response went down. Most patients in stage II-B showed complete response while in stage III-B, only 5% patients and in stage IV, only 2.6% patients showed complete response. Eight percent patients, who had failure of treatment, is because of bulky size tumor and dose limitatations to the pelvis due to critical organs, i.e. the urinary bladder and rectum. Most of our patients had haemoglobin around 10 gm%, translating into poorer response to treatment.

In a study by Sing *et al.,* treatment response after chemoradiation was 93.0%, 79.1%, and 13.9%, as total response, complete response and partial response, respectively and with radiation alone dropped as 90.2%, 58.5% and 31.7%, respectively.[17]

Yet another study done by Negi *et al*. did not show any benefit of concurrent chemoradiation as compared to radiotherapy alone in locally advanced cervical cancer patients. The difference in complete response in the study and control group was statistically not significant (p=0.736).[18] In another study, Pearcy could not find significant difference in outcome with concurrent chemoradiation over RT alone (60% for CRT arm versus 56% for RT alone arm).[19] In the study by Kundu, cisplatin-based chemoradiation was found to be more effective (55.56% vs. 48.89%, p = 0.67) in terms of complete response as compared to gemcitabine-based chemoradiation, although statistically insignificant.[20]

In the study by Ozsaran *et al*., chemoradiation provided high response rates where 76.9% had complete response, 20.5% had partial response and 2.6% had stable disease.[21]

In a meta-analysis that compared chemoradiotherapy versus radiotherapy, there was a 6% improvement in 5-year survival with chemoradiotherapy (hazard ratio [HRI = 0.81, p < 0.001).[22]

A review by Green *et al*. strongly suggests chemo-radiation improves overall survival and progression-free survival, whether or not platinum was used with absolute benefits of 10% and 13%, respectively.[23]

In this study, gastrointestinal toxicity was the principal adverse effect followed by genitourinary and neutropenia. Gastrointestinal toxicity was also higher in the studies by Kundu and Sheheryar.[14,20] However, in the study by Sing *et al*., most common toxicity was hematological (20.9%) followed by gastrointestinal (13.9%).[17]

On the basis of good overall response rate shown in this study and acceptable toxicity, cisplatin-based concurrent chemoradiation seems to be an effective treatment in locally advanced carcinoma of cervix. The authors attribute the following factors for the relatively poor response in these patients such as bulky central disease, anemia and undue gaps in in-between radiation treatment.

CONCLUSION

Cisplatin-based concurrent chemoradiation showed good overall response rate in patients with locally advanced squamous cell carcinoma of cervix and it was well tolerated by the patients.

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