ORIGINAL ARTICLE

Efficiency of Cisplatin Based Concurrent Chemoradiation in Stages III & IV Head & Neck Squamous Cell Carcinoma

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ABSTRACT

Objective: To determine the response of cisplatin based concurrent chemoradiation in stages III and IV head & neck squamous cell cancer and to evaluate frequency of common toxicities.
Introduction: Almost 70% of head and neck cancer patients present with locally advanced disease (stage III and IV). Concurrent chemo-radiotherapy is the current standard treatment. Cytotoxic cisplatin is the treatment of choice for concomitant chemoradiotherapy. Cisplatin acts as a radiation sensitizer and advances the anti-tumor efficacy when combined with radiotherapy. Likewise all chemotherapeutic agents also show side effects including mucositis, dermatitis, nausea & diarrhea.
Materials & Methods: A descriptive study conducted in Department of Radiotherapy, Karachi Institute of Radiotherapy and Nuclear Medicine from 2010 to 2011. Fractions with 2 Gy per fraction were completed in 7 weeks. Sample size of 85 enrolled. Total dose of radiotherapy was 66 Gy in 33 fractions. Cisplatin of 100 mg /m² on day 1, 22 and 43 were given. Treatment response was determined radiologically at four weeks. Toxicity was assessed weekly during treatment.
Results: Mean age was 55.4 (±10.5) years with Male to Female ratio was 1.3: 1. Thirty (41.1%) patients had achieved complete response (CR), 36 (49.3%) patients had partial response (PR). Significant response rate was 90.4%. p-value was siginficant <0.05. Most common toxic effects were mucositis 72.6%, vomiting 68.5%, moderate dermatitis 64.4% followed by mild diarrhea 60.3% and dry mouth 54.8%. Overall response of cisplatin was good.
Conclusion: A significant response of cisplatin based chemoradiation achieved. Mucositis was found the most common toxic effect.

Key words: Head & neck cancer, cisplatin, chemoradiation.

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INTRODUCTION

Head & Neck malignancy is second most common neoplasm in women and third most common in males in Pakistan[1]. Oral cavity tumor in Karachi South ranks second in both genders with similar rates. Karachi Institute of Radiotherapy & Nuclear Medicine (KIRAN) is a complete health care institute not only for diagnosis and treatment of cancers but also a research centre for all cancer. According to the statistic at KIRAN, reported in the last nine years from 2000 to 2008, it ranks the first most common in males (32.6%) and second most common in females (15.1%)[2]. About 70% of head & neck cancer (HNC) are found locally extensive lesions i.e. stage III & stage IV. Despite confined treatment with surgical excision, radiotherapy (RT) or both, <30% of them stay free of disease for three years[3]. Multiple chemotherapeutic regimens have been studied in combination with concurrent RT. Cisplatin is a illustrative chemotherapeutic agent, and it acts as a radiation sensitizer and advances the anti-tumor efficacy when combined with RT[4]. After standard therapy about 30 to 50% of patients with locally extensive lesions survive for three years. Local recurrences or distant metastases develop in 60% patients[5]. Complete survival advantage upto 8% showed in concurrent chemotherapy[6]. Sole cisplatin is cytotoxic agent of preference for parallel chemoradiotherapy[6]. With primary lesion control rates improve; however, distant metastases are fairly more common failure pattern. Residual primary disease, recurrence of tumor or

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appearance of second primary after radiotherapy or surgery and/or chemoradiotherapy is a significant difficulty. However, the most efficacious chemotherapy regimen remains to be recognized[7]. Studies of the 1990s consuming combine chemotherapy with synchronized radiation in squamous cell head & neck carcinoma have proved this treatment method as feasible and have promising outcomes[8]. Adelstein et al used cisplatin and 5-fluorouracil with synchronized split-course radiotherapy. They described 4-years relapse-free survival of 45% and a general survival of 49%[9]. Till now, nobody has undertaken a randomized trial to associate surgery and adjuvant radiation with concurrent chemoradiotherapy as a treatment of locally advanced head and neck neoplasm[8]. Local study done at Nishtar Medical Hospital, Multan showed concomitant chemo-radiotherapy was statistically superior to induction chemotherapy[10]. In view of these studies we planned to evaluate the response of cisplatin based concurrent chemoradiation in locally extensive head and neck cancer at our institute. We determine frequency of response & toxicities of cisplatin based concurrent chemoradiation in locally advanced head & neck squamous cell carcinoma patients. Result of our study enables us to improve our knowledge regarding patient management.

MATERIALS & METHODS

This descriptive study conducted at Department of Radiotherapy, Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN). Ethical committee of the institute has approved this study. A sample size of 85 was calculated with 95% confidence interval and 10% margin of error. Purposive Sampling (Non probability) taken. Sample selection was done under the following set criteria[10].

Inclusion Criteria: All patients of histologically proven locally advanced squamous cell carcinoma of head and neck i.e. stage III to IVB without distant metastases.

Age <70 years and >18 years.

Patients of both genders.

Only patients with Eastern Co-operative Oncology Group (ECOG) performance status between 0-2 (see appendix).

Exclusion Criteria: Previous surgical excision (except biopsy) of effected part previous radiotherapy.

Patients with significantly deranged hepatic and renal functions.

Pregnant patients.

Data Collection & Analysis: Patients fulfilling the eligibility criteria were enrolled in the study through radiotherapy OPD of KIRAN. Informed written consent was taken. Staging was done according to TNM classification of AJCC 2010. Total dose of radiotherapy was 66 Gy in 33 fractions with 2 Gy per fraction was completed in 7 weeks. It was delivered in five consecutive days with two days rest in a week. Cobalt 60 machine was used. Chemotherapy with Cisplatin 100 mg /m² on day 1, 22 and 43 planned. Thermoplastic sheets were used to ensure proper immobilization for accurate delivery of dose and all patients were seen at least once a week during treatment. Treatment response was determined radiologically at four weeks after completion of therapy by comparing pre and post chemoradiation computed tomography (CT) scan jointly by researchers, and was reported. Treatment response was categorized in two different categories using response evaluation criteria in solid tumors (RECIST)[11].

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Complete and partial response were considered as significant outcome

Toxicity Profile: Patients were evaluated weekly for presence or absence of common toxic effects, i.e mucositis- present or absent, vomiting- I vomitus/day**,** diarrhea- <4stools/day or >4stool, dermatitis- mild or moderate, dry mouth- present or absent

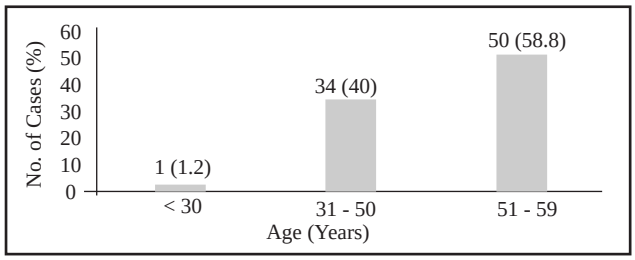
After collection of data, it was analysed using Statistical Package for Social Science (SPSS) version 17. Categorical data like stage of disease gender, response rate and toxicity were expressed in frequency and percentages. For age mean+/- standard deviation was calculated. Effect modifiers were controlled through stratification like age, gender and staging of lesion to see response on it.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

RESULTS

Total of 85 histologically proven locally advanced squamous cell carcinoma of the head and neck (stage III & IVB) patients were included in this study. Forty eight (56.5%) were male and 37 (43.5%) were female (Male: Female = 1.3: 1). Mean (±SD) age of patients was 55.4 (±10.5) years with min – max = 27 – 69 years. Majority of cases 50 (58.8%) had age between 51 – 69 years. (Figure-1)

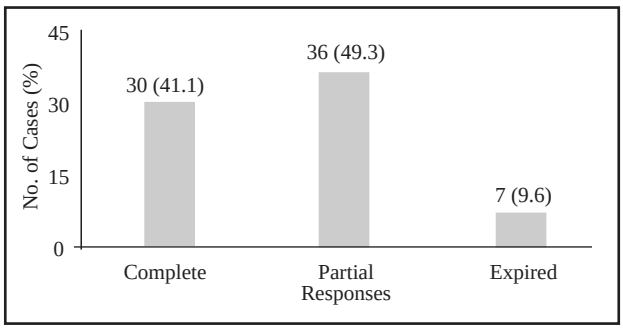
Figure 1: Age Distribution



Mean (±SD) = 55.4 (±10.5) years
Min – Max = 27 – 69 years

Out of 85 cases, 53 (62.4%) patients had stage IV disease while 32 (37.6%) had stage III. There were 7 deaths and 5 dropouts. All 12 cases were considered as treatment failure, and were excluded from the response analysis. Seventy three (73) patients were studied for the treatment response, 30 (41.1%) patients had attained complete response (CR), 36 (49.3%) patients had partial response (PR) and 7 (9.6%) showed no response. The significant response rate (complete response plus partial response) was 90.4%. (Figure-2) p value was significant <0.05.

Figure 2: Response of Concurrent Chemo-radiation in Locally Advanced Squamous Cell Carcinoma of the Head and Neck (n=85)



Toxic effects and their magnitudes observed during the study are listed in Table-1. The most common toxic effects were found mucositis 53/73 (72.6%), vomiting (> 1 vomiting / day) in 50/73 (68.5%), moderate dermatitis in 47/73(64.4%) followed by mild diarrhea (< 4 stool / day) in 44/73 (60.3%) and dry mouth in 40/73 (54.8%)

Response rate was high in males. Twenty one (43.8%) male and 15 (40.6%) female had achieved partial response while 18 (37.5%) male and 12 (32.4%) female had achieved complete response. (Table-2)

Response of concurrent chemo-radiation with respect to age is shown in Table-3. Partial and complete response was high in age between 31 – 50 years.

Response of concurrent chemo-radiation with respect to stages of carcinoma is shown in (Table-4).

Table 1: Common Toxicities of Concurrent Chemoradiation (n=85)

	No. of Cases	Percent (%)
Mucositis	53	72.6
Vomiting		
1 vomiting	23	31.5
> 1 vomiting	50	68.5
Diarrhea		
< 4 Stool	47	64.4
> 4 Stool	26	35.6
Dermatitis		
Mild	44	60.3
Moderate	29	39.7
Dry Mouth	40	54.8

Table 2: Response of Concurrent Chemo-radiation with Respect to Gender (n=85)

Response	Male n=48	Female n=37
Complete	18 (37.5%)	12 (32.4%)
Partial	21 (43.8%)	15 (40.6%)
No Response	4 (8.3%)	3 (8.1%)

Table 3: Response of Concurrent Chemo-radiation with Respect to Age (n=85)

Response	Age (Years)		
	<=30 n=1	31 - 50 n=34	51 - 69 n=50
Complete	0	13 (38.2%)	17 (34%)
Partial	0	18 (52.9%)	16 (32%)
No Response	1 (100)	0	6 (12%)

Table 4: Response of Concurrent Chemo-radiation with Respect to Stages (n=85)

Response	Stages of Squamous Cell Carcinoma	
	III n=32	IV n=53
Complete	17 (53.1%)	13 (24.5%)
Partial	24 (75%)	12 (22.6%)
No Response	3 (9.4%)	4 (7.5%)

DISCUSSION

Radiosensitizer Cisplatin is a strong chemotherapeutic agent and usually used in HNC. The jeopardy of side effects are grade 3/4 renal dysfunction having hazard upto 5%, grade 3/4 neurological toxicity with risk ~5%, & intense vomiting, sickness; problem found upto 25%. These problems are common with cisplatin 100 mg/m^2 dosage every three weeks. Upto 85% of patients suffered with mucositis (grade ¾) but most were manageable. Renal side effects reduced if people have a normal creatinine clearance. A meta-analysis revealed survival benefit found in platinum-containing chemotherapy agent[12]. To reduce toxicity, substitute alternating regimens are also used. e.g., once weekly reduced cisplatin doses are much less lethal than 100 mg/m^2 cisplatin every three weeks. Dose of 30 mg/m^2 cisplatin , no toxic input on kidneys were observed, rather inflammation of oral mucosa and neutropenia were found significant[13]. As there is not much evidence, so usage of cisplatin weekly would be restricted to medical trials and to those who are not able to bear normal regimen. Hypothetically, once weekly administration of cisplatin has ability to improve radio sensitization, but evidence is desirable to support this proposition. To reduce nephrotoxicity, cisplatin could be consumed as daily infusion about 20 mg/m^2 on days 1 to 4 in weeks first and fourth[14]. likewise once weekly cisplatin, effectiveness of this plan is not sufficiently recognized. Doses of 5–8 mg/m^2 daily is feasible as one experiment testified by Jeremic *et al*. consumed dose of 6 mg/m^2 of cisplatin five days every week during radiation[14]. Renal toxicity found in 5% while leukopenia occurred in 12%; So, it is concluded that therapy does not reduces the side effects.

Presently, extensively utilized regular treatment is 100 mg/m^2 cisplatin every three weeks, collective with ~70 Gy radiations deliver in 1.8–2.0 Gy daily. This regimen causes unadorned lethal effects on renal, ear and brain as well as nausea and vomiting and severe mucositis. This makes the therapy appropriate only for those having standard creatinine clearance. Also, loco regional failure is upto 65% that depends on site of tumor, tumor staging & its resectability[15,16]. In 2003 a series revealed that 3-years survival was 37%[9]. In this study, 41.1% patients had attained complete response & 49.3% patients had partial response while 9.6% shown no response. These results were inferior to those reported by Jain et al where CR was reached in 73% of patients receiving paclitaxel and 64% of patients who received cisplatin concurrently with radiotherapy[17]. The inferior results of present study might be due to the observation that the majority of our patients were stage IV, while in Jain's et al., study the majority were stage III, but the difference between the two groups was insignificant in both studies. Frequency of complete response in cisplatin group in our was comparable with Zenda et al., (50%)[18] and Kim et al., (54.2%)[4] but it was more than that reported by Adelstein et al., (40.2%)[9]. It was inferior to that of Vokes et al., (67%)[19], Poole et al., (82%)[20] and Hung et al (77%)[21] but in these studies cisplatin was utilized in combination with other chemotherapeutic drugs. Local study done at Nishtar Medical College/Hospital, Multan, in which the subjects were randomized into three groups**.** Group A: lnduction chemotherapy with cisplatin (100 mg/m2) and 5-FU (500 mg/m2) infusion for 3 days followed by radiotherapy. 70 patients were in this group. Group B: Radiotherapy alone with cobalt 60 (Co60) - 6600 cGy given in 6-7 weeks. 66 cancer patients were included in this group. Group C: Concomitant chemo-radiotherapy. 64 people included in this group. At completion, people in group-A showed a response rate of 39% i.e. complete response in 05% and partial response in 34%; in group-B there were 64% with complete response of 10% and partial response of 54% while in group-C, having complete response in 33% and partial response in 67% of concomitant chemo-radiotherapy in primary extensive head & neck cancer[10]. This research told substantial response rate (complete plus partial response) was 90.4%. A study from Egypt reported the clinical overall response was 75% in concurrent therapy[22]. Another study from India reported significant response of concurrent therapy was 88.5%[23]. Toxic effects were observed during this study. The most common toxic effects were mucositis (72.6%), vomiting (> 1 vomiting/ day) (68.5%), moderate dermatitis (64.4%) followed by mild diarrhea (< 4 stool / day) (60.3%) and dry mouth (54.8%). The degree of these toxicities was comparable to other studies[17,24,25]. Acute toxicity of the multiagent concurrent chemo radiotherapy regimens is suggestively high[26] that essentially needs violent supportive care at hospital. Therefore while recommending CCRT one must realize the lethal effects as combined treatment modality has been related with increased risk of toxicity[27].

Despite acute toxicities, most of our patients completed the intended treatment. 85.8% completed therapy in proposed time. Therefore, this study reflected that synchronized chemoradiotherapy provides high locoregional cure, in the patients of primary extensive squamous cell cancer of head and neck with good functional status. Though this treatment is lethal, but is controllable with vigilant supportive staff. This therapy is possible in our arrangement as skilled manpower in field of supportive care is obtainable.

CONCLUSION

Cisplatin based chemoradiation yields high control in locally advanced squamous cell carcinoma of head and neck with good functional status.

In this study a significant response rate 90.4% *{complete response (41.1%) plus partial response (49.3%)}* of cisplatin based concurrent chemotherapy was achieved. Mucositis was the most common toxic effect found while dry mouth was the least common toxic effect.

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