EFFICACY OF INDUCTION CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK

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ABSTRACT

Objective: To determine the efficacy of induction chemotherapy in locally advanced squamous cell carcinoma of head and neck.

Study Design: Descriptive case series.

Place and Duration of Study: This study was conducted at the Department of Oncology, Combined Military Hospital (CMH) Rawalpindi, from Feb 2016 to Aug 2016 over a period of 6 months.

Material and Methods: Fifty five patients of both genders, having ages 12-65 years with confirmed histo-pathological diagnosis of squamous cell carcinoma of head and neck region with clinical and radiological stage III to stage IVB were included in this study. The patients fulfilling the inclusion criteria were planned to receive 3 cycles of induction chemotherapy and were evaluated after 4 weeks for response assessment. The collected data was analyzed by using SPSS version 17.

Results: Among fifty five patients with Head and Neck Squamous Cell Carcinoma (HNSCC) 34 (62%) patients showed efficacy more than 50%, while, 21 (38%) had no response. Higher efficacy was noted in patients of younger age, male gender, those who were married, with higher literacy level and better socioeconomic status. Higher efficacy was also observed in the patients who had been having HNSCC of less than 12 months (p=0.0031). On univariate analysis, the prognostic factors significantly affecting progression-free survival were marital status and duration of illness.

Conclusions: The efficacy of induction chemotherapy in locally advanced squamous cell carcinoma of head and neck is encouraging and needs further validation through more detailed multicenter trials.

Keywords: Efficacy, Induction chemotherapy, Squamous cell carcinoma.

INTRODUCTION

Head and neck cancer is one of the commonest malignant tumors, with approximately 500,000 new cases diagnosed each year. Squamous cell carcinoma (SCC) is the predominant histological type[1]. The disease is potentially curable at an early stage[2] but about 60% cases present with advanced stage disease. Therefore the prognosis for this form of cancer is still dismal at present and the recurrence rate ranges from 10% to 40%[1].

The treatment strategies for patients with locoregionally advanced HNSCC have moved away from poorly effective single modality therapy and now encompass a multimodality approach (surgery, chemotherapy, radiotherapy and targeted molecular therapeutics)[2,3]. Combined modality approaches have been developed in an effort to enhance locoregional disease control, reduce distant metastatic spread and improve survival in patients with locally advanced inoperable head and neck cancer[2,4]. Among the patients who are candidates for non-surgical therapy, concurrent chemoradio-tharapy (CCRT) is a standard of care, with improvement in overall survival[5], locoregional tumor control and functional organ preservation[6].

Although CCRT has the potential to cure advanced stage disease, a significant number of patients will relapse, particularly those with higher nodal status at presentation[4]. Since head and neck cancers are chemosensitive

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malignancies[7], the introduction of induction chemotherapy followed by CCRT has several theoretical advantages, including reduced risk of distant failure/metastasis, induction of tumor shrinkage to allow more effective and less toxic local therapy, and prediction of tumor response[8]. The overall response rates of HNSCC to induction chemotherapy reaches approximately 86%[4].

The number of patients registering at our hospital with this malignancy is quite high (an average of 20 patients/month), there is a waiting period for the patients before they undergo CCRT. The rationale of the study using induction chemotherapy before standard CCRT is to prevent disease progression during this waiting period. Induction chemotherapy followed by CCRT if proved effective will also identify the patients who would respond well to radiotherapy. It would be helpful to devise a protocol in our set up that would give a good objective response.

MATERIAL AND METHODS

This was a descriptive case series conducted at the Oncology Department of Combined Military Hospital (CMH), Rawalpindi for six months from February 2016 to August 2016. This study was an independent project of the department and was not funded by any pharmaceutical organization. Informed consent was obtained from all patients. A series of 55 successive patients admitted to the department and fulfilling the inclusion criteria were enrolled. Patient of either gender between the ages of 12-65 years with confirmed histopathological diagnosis of squamous cell carcinoma of head and neck region (sub sites: Buccal mucosa, Tongue, Nasopharynx, Oropharynx, Hypopharynx and larynx) with clinical and radiological stage III to stage IVB according to AJCC (American Joint Committee on Cancer) Staging Manual 7th edition were included. Key exclusion criteria included: any evidence of relapse or distant metastases, histopathology other than World Health Organization classification, uncontrolled life threatening co-morbidities and ECOG performance status of III/IV and patients on any other anti cancer treatment, except for SCC or basal cell carcinoma (BCC) of the skin.

After the approval from the Ethical Committee of CMH Rawalpindi, the patients were evaluated in detail on the basis of history, examination and investigations including complete blood picture, serum biochemistry, echocardiography, chest x-ray, abdominal ultrasound, bone scan (for metastatic workup), computerized tomography scans from the base of skull to thoracic inlet. They were then planned to receive 3 cycles of induction chemotherapy under supervision with a 3 week gap in between the cycles. Following drugs were included in chemotherapy cycle:

1) Inj Docetaxel 75mg/m^2 Day 1
2) Inj Cisplatin 75mg/m^2 Day 1
3) Inj 5-Fluorouracil 1000mg/m^2 Day 1-4

The patients were examined/ monitored during induction chemotherapy and were re evaluated (clinically and radiologically) one month after completion of 3 cycles of induction chemotherapy for response assessment.

Data Analysis

The collected data were analyzed by using SPSS Version 17, for quantitative data such as age, mean ± SD would be presented, for categorical variables such as gender, CT scan findings to detect response, frequency tables would be presented. Categorical variables were shown by using the Pie chart and Bar chart. Effect modifiers like age, gender and stage of disease were controlled by stratification. For post stratification chi square test was applied. A *p*-value ≤0.05 was considered to be significant.

RESULTS

A total number of 55 patients were included in the study. The mean age was 39.10 ± 26.46 years with a male preponderance (78%). The baseline characteristics of study population are shown in table.

Among 55 patients with HNSCC 34 (62%) patients showed efficacy more than 50%, while, 21 (38%) had no response (figure).

More than 50% efficacy was seen in 66% patients of age range from 15-20 year, 71% patients of age range from 21-30 years, 70% patients of age range from 31-40 years and 71% patients of age range from 41-50 years (p=0.794). In gender 63% of male patients had more than 50% efficacy while 58% of female patients had more than 50% efficacy (p=0.78). Our study showed that when stratified according to education level more than 50% efficacy was seen in 30% of patients having their education up to primary level, 71% of patients having their education up to middle class, 72% of patients having their education up to matriculation, 57% of patients having their education up to intermediate level and 83% of patients having their education up to post graduate level (p=0.943).

Table: Baseline characteristics of study patients (n=55).

Age (years)		
Mean ± SD	39.10 ± 26.46	
Range (min-max)	12-65 years	
Age Categories (Years)	**Number of patients**	**Percentage of Patients**
12 to 20	03	5.5
21 to 30	07	12.8
31 to 40	10	18
41 to 50	13	23.6
51 to 60	11	20
61 to 65	11	20
Gender		
Male	43	78
Female	12	22
Marital Status		
Married	35	63
Unmarried	20	37
Socioeconomic Status		
Poor	12	22
Middle class	27	49
Upper class	16	29
Education Status		
Primary	13	23.6
Middle	11	20
Matriculation	18	32.7
Intermediate	07	12.7
Post-graduate	06	41.1

Stratification in terms of socioeconomic status revealed that 41% of patients having poor socioeconomic status had more than 50% efficacy while this level of efficacy was seen in 60% of patients belonging to middle class families and 81% of patients belonging to high class families (p=0.095). In our 65% patients who were married had more than 50% efficacy while 55% patients who were unmarried had more than 50% efficacy (p=0.046). When stratified according to the duration of illness; more than 50% efficacy was seen in 63% of patients having HNSCC of less than 6 months, 70% of patients having HNSCC of 6-12 months and 20% of patients having HNSCC of more than 12 months (p=0.0031).

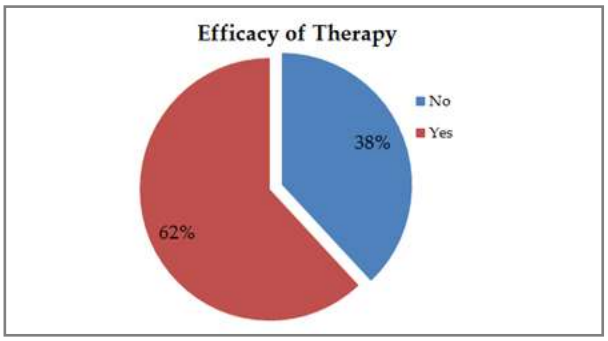

Figure: Efficacy of induction chemotherapy.

DISCUSSION

Head and neck squamous cell carcinoma (HNSCC) comprise 3-5% of total cancers and more than 60% of patients are referred at advanced stage of disease. Conventional treatment plan for loco-regionally advanced cancers is surgery followed by adjuvant radiotherapy. In patients who defer surgery or are not fit for the procedure, radiotherapy/ chemoradiation is used as the standard defini-tive treatment[9]. The role of induction chemo- therapy remains controversial. However since chemotherapy can potentially reduce the tumor size, lower the risk of distant metastasis and improve feasibility and tolerability of radiation, it continues to be investigated in trials and discussed in reviews.

In a study by Jan *et al* Induction therapy was given and the patients had a reduction of 28% in the risk of disease progression or death[10]. The response rate in our study with the same combination of induction therapy was much higher at 62%. Their study like our study showed a much higher male preponderance of this particular cancer (90% v.s 78%). However, gender had no significant effect on the efficacy of chemotherapy. Majority of the patients were above 40 years of age. But age again had no role as far as the response to treatment was concerned.

In a study by Won *et al* 52 patients were retrospectively evaluated; 12 patients received 5-fluorouracil-plus-cisplatin (FP); 24 patients received docetaxel-plus-cisplatin (DP); 16 patients received docetaxel, cisplatin, and 5-fluorouracil (TPF). The TPF regimen showed a trend towards a higher overall response rate and pathological complete response and led to a significantly higher rate of metabolic complete response. On univariate analysis, the prognostic factors significantly affecting progression-free survival were lymph node stage, and metabolic and pathological complete response[11]. While in our study significant prognostic factors were marital status and duration of illness.

A multicenter non-comparative pilot study of locally advanced squamous cell carcinoma of the head and neck was performed by Noronha and his colleagues. Patients received primary therapy comprising three cycles of 75 mg/m^2 docetaxel and 75 mg/m^2 cisplatin followed by concurrent chemoradiotherapy. The primary endpoint was the response rate to the docetaxel and cisplatin induction regimen. The overall response rate to docetaxel and cisplatin induction chemotherapy was 65.4% which is much closer to our results[12].

More than 60% of patients diagnosed with HNSCC present at a locally advanced stage. Although multimodality therapy has improved locoregional control, the 5-year survival rate of this population rarely exceeds 30%. The Meta-Analysis of chemotherapy in Head and Neck Cancer collaborative group has suggested a survival advantage of 5% at 5 years for platin 5 fluorouracil induction chemotherapy. Meta analysis showed that cofactors that may affect the survival of head and neck patients and propose new end points for assessment of the efficacy of induction chemotherapy. We have examined the impact of new cytotoxic agents and present the promising results of new taxane-based combinations[13].

Concurrent chemoradiotherapy (CCRT) has been considered to be the standard of care for locally advanced squamous cell carcinoma of head and neck (LA-SCCHN). Whether induction chemotherapy (IC) with CCRT will further improve the clinical outcomes or not is still unclear. A meta-analysis was conducted to compare the two regimens for LA-SCCHN. Five prospective randomized controlled trials (RCTs) with 922 patients were included in meta-analysis. Compared with CCRT, IC with CCRT showed no statistically significant differences in overall survival (OS), progression-free survival (PFS), overall response rate (ORR) or locoregional recurrence rate (LRR), but could increase risks of grade 3-4 febrile neutropenia (p=0.0009) and leukopenia (p=0.04). In contrast, distant metastasis rate (DMR) decreased (p=0.006) and complete response rate (CR) improved (p=0.010) for IC with CCRT. In conclusion, the current studies do not support the use of IC with CCRT over CCRT, and the further positioning of IC with CCRT as standard treatment for LA-SCCHN will come from more RCTs directly comparing IC followed by CCRT[14].

The trial by Bonner *et al* demonstrated a 10% overall survival (OS) benefit when cetuximab was added to radiation in the treatment of locally advanced head and neck squamous cell carcinoma, and it led to acceptance of cetuximab-based combined modality therapy as a standard of care. Of interest, cetuximab was not shown to worsen common acute radiation toxicities such as mucositis, dysphagia, or pain. Therefore, it was

considered the rare drug that improves survival without substantially increasing toxicity[15].

Chenming and his colleagues performed seven randomized clinical trials in which they included patients with advanced head and neck cancer who underwent induction chemotherapy with either a Tax-PF or PF protocol. In terms of 3-year and 5-year overall survival and progression-free survival, overall response rate and different types of adverse events patients in the Tax-PF group were statistically superior to those in the PF group. In terms of toxicities, the incidence of febrile neutropenia, alopecia and leukopenia was higher in the Tax-PF group. The Tax-PF induction chemotherapy was better as compared to PF-based therapy regimens at the cost of a higher incidence of adverse events[16]. We did not study adverse effect profile.

Our study was limited because it was a single center study with short study period and we did not include analysis and documentation of the adverse effects of chemotherapy.

CONCLUSION

The efficacy of induction chemotherapy in locally advanced squamous cell carcinoma of head and neck is encouraging and needs further validation through more detailed multicenter trials.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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