Original Article

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Oncology Section

Induction Chemotherapy with Cisplatin and 5-Fluorouracil in Advanced Head and Neck Cancers: A Short Term Response Evaluation

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ABSTRACT

Background: Considering the uprising number of Head and neck cancer in the state with limited options of medical and surgical treatment, the focus of this study involved on chemotherapy in advanced Head and neck cancers. The aim of this study was to evaluate the efficacy and toxicity of combination of Cisplatin and 5-Fluorouracil (PF) as induction chemotherapy in patients in locally advanced squamous cell cancer of head and neck.

Materials and Methods: Forty four patients with previously untreated stage III -IV advanced and inoperable cases were included in this prospective study. Induction chemotherapy consisted of 3 cycles of Cisplatin 100mg/mt^2 as infusion on day 1, 5-Fluorouracil of 750mg/mt^2 on day 2, 5-Fluorouracil of 1000mg/mt2 as infusion on day 3 in an inpatient basis. Cycles were repeated with an interval of 21 days. Patients were evaluated within a period of 3 weeks at the end of completion of third cycle of chemotherapy. Post chemotherapy local therapy was individualized based on the response, site and stage of the tumour.

Results: Out of 44 eligible and evaluable patients, major dominance was noted in male group constituting 68%. After induction chemotherapy 58.8% of stage III experienced stable response, & 44% had partial response. In stage IV, 44% showed a stable response and 33.3% had partial response. But in comparison to primary tumour response and nodal response, which had a significant clinical response, the overall response of malignancy with respect to stage and site specificity was clinically insignificant. Moderate adverse reaction was noted in 47.6% and 42.1% had mild reactions. Majority of patients experienced grade 3 adverse events, of which anaemia in females and leucopenia in males pre-dominated.

Conclusion: With the use of cisplatin and 5-FU as induction chemotherapy agents in advanced and inoperable squamous cell carcinoma of head and neck, a distinct benefit was seen in stabilizing the tumour from progression. But achieving a significant complete response to the same is of faint possibility. An alternate multidrug regimen or multimodality treatment would be ideal to gain the optimum results from induction agents. Toxicity related to chemotherapy usually is transient at therapeutic doses, and can be controlled by adequate prophylactic measures.

Keywords: Adverse effects, Squamous cell carcinoma of head and neck (SCCHN), Tumour response

INTRODUCTION

Head and neck cancer is a fatal disease with an increased morbidity and mortality rate. It comprises of epithelial malignancies of the upper aerodigestive tract (UADT), paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx. Occupying at sixth position among all cancers worldwide, annually approximately 550,000 people are diagnosed with head and neck cancers and 300,000 people have succumbed to death with a median age of diagnosis during the sixth decade of life [1].

Head & neck cancers are vastly debilitating condition that are associated with difficulties in eating, chewing, drinking, breathing, speaking, as well as changes in appearance. Despite recent advances in surgical techniques, radiation therapy, chemotherapy, combined modalities survival data has not showed appreciable results. Two third of the patients present with locally advanced lesions (stage 3 & 4) and in these patients, the survival rate at 5 years is <30% in spite of use of more radical surgery and /or radiotherapy [2-4].

The accession of chemotherapy to locoregional treatment has upheaved the treatment of patients with advanced squamous cell carcinoma of the head and neck (SCCHN). Large meta-analysis of individual patient data from previously endorsed randomized trials have proved that combining chemotherapy has led to a survival benefit of around 4% at 5 years in comparison with locoregional treatment alone [5,6].

Chemotherapy had been investigated in both the induction and adjuvant settings as well as concomitantly with radiotherapy. Induction chemotherapy is the use of drug therapy as the initial treatment for patients presenting with advanced cancer that cannot be treated by other means. Multiple induction regimens have been tried with drugs like Cisplatin, 5- Fluorouracil, Methotextrate, Carboplatin, Paclitaxel, Docetaxel as 3 cycle dose/5 cycle dose with variable results. Here, we have analysed the efficacy and toxicity of Cisplatin and 5-FU induction regimen in advanced SCCHN.

MATERIALS AND METHODS

This study was a prospective type. A total of 44 cases with advanced squamous cell carcinoma of head and neck were studied during the period of October 2011 to September 2013 in the Department of Otorhinolaryngology – Head and Neck Surgery, KMC Hospital, Attavara and Government Wenlock Hospital, Mangalore, India.

Inclusion criteria: (i) Age > 30, <80 years; (ii) Sex – both male and female; (iii) Newly diagnosed patients & previously untreated cases; (iv) Advanced stage 3 & 4 head and neck cancers including

oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, nose & paranasal sinuses, metastasis of unknown origin; (v) Biopsy confirmed Squamous cell carcinoma of head & neck; (vi) Patients who were willing to get admitted and receive chemotherapy.

Patients with previous history of any major surgery within a period of one year, presence of major co-morbid illness (Infective and immunosuppressive diseases like TB, HIV, uncontrolled diabetes, uncontrolled HTN, chronic renal disease at the time of diagnosis), Unscheduled hospitalization in-between, Squamous cell Carcinoma of cutaneous, salivary gland, esophageal origin were excluded from the study.

Each patient included in the study was evaluated thoroughly by detailed history, detailed head & neck as well as systemic examination. With the help of Karnofsky score [7] patient's general condition was evaluated. The relevant investigations that included a complete blood picture, ESR, RFT (urea & creatinine), LFT (AST, ALP), serum electrolytes, chest X ray, ECG, ultra sound neck and abdomen and CT scan of the head and neck was routinely done in all patients. An FNAC was done in all palpable lymph nodes in head & neck. Necessary endoscopic examinations including sinuscopy, nasopharyngoscopy, direct laryngoscopy, 70 degree telelaryngoscopy, esophagoscopy were done considering the site of malignancy.

All the 44 patients were evaluated by a multidisciplinary team that included medical oncologist, head and neck surgeons, radiologists, and pathologists so as to confirm the eligibility, staging and treatment planning. Patients were assigned a clinical stage according to the criteria of the American joint committee on cancer. Tumour unresectability/advanceness/inoperability was assessed at this stage based on the following criteria [8]:

(i) Extensive oral cavity tumours whose resection would deter functional reconstruction.

(ii) Tonsil tumours extending into the pterygoid region or extending across the midline of the pharyngeal wall or directly infiltrating into soft tissues of the neck.

(iii) Base of tongue tumours requiring total glossectomy or infiltrating into the root of the tongue.

(iv) Laryngeal tumours infiltrating directly into adjacent muscle or skin, or with subglottic extension of >3cm, or involving prevertebral fascia.

(v) Hypopharyngeal tumours crossing the midline of the posterior pharyngeal wall or involving prevertebral fascia, Fixity of the tumour to the cervical spine or involving mediastinal structures.

(vi) Fixity of metastasized neck nodes to the carotid artery, mastoid, skull base, or cervical spine.

(vii) PNS tumours invading any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve, nasopharynx, or clivus.

A histopathological confirmation by taking biopsy was made in all cases prior to start of chemotherapy. Based on the American Joint Commission on Cancer guidelines for grading tumours a histopathological grading was done as described in [Table/Fig-1]:

Induction chemotherapy: The regimen followed was use of pre-medication drugs followed by chemotherapeutic drug. Pre-medication drugs: Inj. Dexamethasone of 4-8mg; Inj. Rantac 50mg; Inj. Emeset 8mg in 100 ml NS over ½ hour.

Day 1: pre-medication followed by Inj.Cisplatin100 mg/sq.mt in 500ml ns over 2hours.

Day 2: pre-medication repeated followed by inj. Fluorouracil 750mg/sq.mt in 500ml NS over 20 hours.

Day 3: pre-medication repeated followed by inj. Fluorouracil 1000mg/sq.mt in 500ml NS over 20 hours.

GRADES	
GX	Grade cannot be assessed (Undetermined grade)
G1	Well-differentiated (Low grade)
G2	Moderately differentiated (Intermediate grade)
G3	Poorly differentiated (High grade)
G4	Undifferentiated (High grade)

[Table/Fig-1]: Grades of histological tumour differentiation [8]

Chemotherapy was started within a period of 3 weeks of study entry as an in-patient basis after confirming the normalcy of baseline investigations. Adequate hydration was maintained and patients were monitored for toxicity (medical interview, physical examination and complete blood counts) during their hospital stay. The same chemotherapeutic regimen was repeated at 3 week interval for a total of 3 cycles.

Following parameters was evaluated at the time of diagnosis & after completion of 3 cycles of chemotherapy within a period of not more than 3 weeks: (i) History and clinical examination: symptoms, signs, tumour size/extent, lymph node size; (ii) CT scan/USG quantification of tumour/nodal Size; (iii) Relevant Laboratory investigations: Hb%, CBC, RFT, LFT; Electrolytes (iv) Adverse effects.

Response grading	Criteria met
Complete	Disappearance of tumour completely either clinically or radiologically.
Partial	More than 50% reduction in the size of tumour in more than two dimensions either physically or radiologically.
Stable	No significant change in dimensions, less than partial response but no evidence of disease progression.
Failure	More than 25% enlargement in tumour after completion of 3 cycles of chemotherapy.

[Table/Fig-2]: Response grading of malignancy post chemotherapy [9]

CT and clinical response grading was done accordingly [Table/Fig-2].

Adverse events during the chemotherapy were evaluated based on common toxicity criteria (edition CTCAE version 4) developed by National cancer institute. For each adverse event, grades are assigned and defined using a scale from 0 to 5 (mild – death related to adverse event). After the completion of chemotherapy patient was assessed for response and based on the increase/decrease of the growth further treatment with radiotherapy or surgery or palliative chemotherapy or combined modality was persuaded.

STATISTICAL ANALYSIS

The sample size was calculated with an 85% power (ß = .2) and a two-sided significance level of α = .05. Patient characteristics, toxicity, and response rates in the two treatment arms were compared using the Student's t-test for continuous variables and the χ^2 test for categorical variables.

RESULTS

Fifty five patients diagnosed with advanced SCCHN during the period of October 2011 to September 2013 was enrolled in our study. All the patients in the study group received 3 cycles of induction chemotherapy with Cisplatin and 5-FU only after considering the patients general condition, biopsy report, and eligible criteria.

Eleven patients were excluded from our study because three had poor Karnofsky performance score (<50). Four patients interrupted therapy after one or two cycles of induction and were considered as invaluable for assessing response. Two patients were hospitalized in-between for the treatment of cardiac illness; hence their chemo treatment was delayed. Two were lost to follow up during the induction therapy. As all these were considered as protocol violation these patient were excluded in the study.

Gender				
Male	30 (68.2%)			
Female	14 (31.8%)			
Age (yrs)				
Range	29-80			
Median	60			
Stage III	17			
Stage IV	27			
	NO	**N1**	**N2**	**N3**
TX	0	0	2	0
T1	0	2	0	0
T2	1	3	2	0
T3	3	10	9	0
T4	1	4	6	1
Site				
Oral cavity	12			
Oropharynx	9			
Larynx	12			
Hypopharynx	7			
Nose & PNS	2			
MUO	2			

[Table/Fig-3]: Pretreatment characteristics of eligible and evaluable patients (n=44)

In our study maximum number of patients was seen in the age group of 51-70 years. With a mean age of incidence equals to 60. Patients whose karnofsky status was <50 were excluded from study as general condition of the patient withholds the start of chemotherapy. Among the 44 patients, 14 were female, and 30 were male patients. Males were predominated in all sites of malignancy. A 47.7% patients had Karnofsky score of 70, implying majority of patients were capable to care for self but unable to do or perform daily activity.

As described in the [Table/Fig-3], majority of patients (61.4%) presented to us in stage IV malignancy followed by (38.6%) stage III. Oral cavity and laryngeal tumours constituted up to 27.3%, oropharynx 20.5%, hypopharyngeal 15.9%, PNS and MUO constituted 2% of the head and neck cancers included in our study. The histological differentiation was described as moderately differentiated in 22 cases (50%), poorly differentiated in 15(34.1%) and well differentiated in 7 cases (15.9%).

Efficacy of the treatment regimen: When compared to females, 42.9% having a stable and 28.6% partial response to chemotherapy; 53.3% male patients showed a stable response with 33.3% showing partial response. Even though male patients showed a better response, overall there was no significant response change to chemotherapy with respect to gender (p=0.489).

Out of 17 stage III patients, 10 showed a stable response (58.8%), 5 partial response and 2 treatment failure (11.8%). And in case of 27 patients who had stage IV malignancy, 12 had stable response (44%), 9 had partial response (33.3%) and 5 patients (18.5%) had treatment failure. There found to be no difference in overall response to chemotherapy with reference to stage of the malignancy (p=0.84).

Analysis of response to various histopathological differentiation of malignancy showed partial response of 57.1% in case of moderately differentiated tumours, 14.3% in poorly differentiated tumours, and 28.6% in well differentiated squamous cell carcinomas. A stable response was seen in 45.5% of moderately differentiated, 73.3% of poorly differentiated and 14.3% of well-differentiated tumours. Treatment failure was majority seen well-differentiated tumours constituting 28.6% followed by moderately differentiated (13.6%) and poorly differentiated tumours (13.3%). Overall less response to chemotherapy was seen in cases of well differentiated squamous tumours.

Primary tumour response evaluation to induction therapy showed a highly significant response in controlling the progression the tumour (p=0.00) with 22 cases showing a stable response (52.4%), 12 cases having a partial response (28.6%), and 1 case had a complete response (2.4%). Nodal response evaluation for chemotherapy also showed a significant reduction in the size or the bulk (p=0.00). Out of 39 nodal positive patients, 22 cases (50%) had stable response, 14 cases (31.8%) had partial response and 1 had complete disappearance of the node.

Overall response evaluation after three completed cycles of chemotherapy showed 31.8% achieving partial response, 50% stable response, 15.9% failure to respond and only 2.3% of patients having a complete response. Partial response was best achieved in cases of oropharyngeal (28.6%) followed by laryngeal and oral cavity malignancies (21.4%). 31.8% achieved stable response in oral cavity malignancies followed by 27.3% in case of oropharyngeal cancers. With the p-value of 0.99 there was no statistical significant overall response (considering both the primary site and the lymph node status) to induction chemotherapy.

Adverse effects grading: Majority of our patients experienced moderate (47.6%) and mild (42.1) adverse reactions related to induction chemotherapeutic agents. No severe nor death related adverse event was seen during chemotherapy. Nonspecific/unlikely/unrelated symptoms were also included during study. Even though 50% of patients had nonspecific symptoms, major adverse events related to chemotherapeutic drugs noted were disturbed haematological parameters followed by asthenia and anorexia. Some toxicity related to chemotherapeutic agents was encountered in all patients but only few were consistent with all the 3 cycles of chemotherapy as shown below in [Table/Fig-4,5].

	No. of patients	%
ANAEMIA	17	38.6%
LEUCOPENIA	15	34.1%
THROMOCYTOPENIA	12	27.3%
MUCOSITIS	11	25.0%
NAUSEA VOMIT	9	20.5%
RENAL	7	15.9%
SKIN	5	11.4%
NEUROLOGIC	4	9.1%
ELECTROLYTE IMBALANCE	9	20.5%
ASTHENIA	15	34.1%
ANOREXIA	13	29.5%
ALOPECIA	4	9.1%
OTHERS	22	50.0%

[Table/Fig-4]: Adverse events during induction chemotherapy

Weight loss	8	36.4
Constipation	4	18.2%
Loss of taste	1	4.5%
Myalgia	5	22.7%
Diarrhea	3	13.6%
Excess sweating	1	4.5%
Total	22	100%

[Table/Fig-5]: Other non-specific adverse events included

DISCUSSION

The non-surgical management of squamous cell carcinoma of head & neck has always been an area of constant interest in medical research. Over the years, multiple varied clinical trials involving small to large population as study group, from single drug regimen phase

I & II studies to multidrug regimen phase III trials and from single modality to multimodal/ combined treatment regimens have evolved eventually. Incorporation of chemotherapy has proved beneficial in oncology, beginning from untreated solid tumours to the recurrent, unresectable metastatic tumours. The rationale for use of induction chemotherapy was based on the increased responsiveness to chemotherapy seen in the previously untreated patient and the possibility that chemotherapy-induced tumour shrinkage might improve local control [10,11].

In a trial designed to determine whether intensive induction chemotherapy administered before loco-regional treatment would improve survival of patients by Paccagnella A et al., with previously untreated, advanced nonmetastatic (stages III and IV) SCCHN showed there were no significant differences in loco-regional failure or in disease-free or overall survival between the patients receiving initial chemotherapy (Cisplatin and infusional fluorouracil with 5 day regimen course for 3 cycles) followed by loco-regional treatment and loco-regional treatment alone strategies, although the development of distant metastases was reduced in the former group. They also showed for operable patients, the only benefit from chemotherapy was a significant reduction in the incidence of distant metastases and for inoperable patients, chemotherapy improved local control, decreased the incidence of distant metastases, and improved the complete remission rate and overall survival [2].

In our study at a median follow up of 3 months, PF showed an individual decrease in the tumour and the nodal burden, but overall response of induction agents in controlling the malignancy was insignificant. Thus, the PF regimen has showed shrinkage in tumour and nodal burden, the % of complete response i.e. complete regression of the tumour is very low. Primary tumour response to induction therapy showed effective response in controlling the progression of the tumour in 22 cases showing a stable response (52.4%), with 12 cases having a partial response (28.6%), and 1 case of complete response (2.4%). The lymph Node response for chemotherapy also showed a significant reduction in the size or the bulk. Out of 39 nodal positive patients, 22 cases (50%) had stable response, 14 cases (31.8%) had partial response and 1 had complete disappearance of the node. To obtain an overall response for each patient, the response at the primary tumour and the regional nodes were combined, and the lesser response was taken as the overall response. Similar studies conducted by Charlotte et al., which showed no impact of histopathological differentiation of the tumour [12], our study showed better response of induction therapy in poor and moderately differentiated tumours and more failure rate in cases of well differentiated tumours.

We analysed the option of induction chemotherapy in advanced tumours where treatment options are limited and found that laryngeal carcinoma is one of the most common such malignancy. An analysis of the only phase 3 study which has compared induction chemotherapy, chemoradiotherapy and radiotherapy alone reported that PF induction chemotherapy was equivalent to Cisplatin based chemoradiotherapy and both were significantly better than radiotherapy alone in terms of 5 year survival with an intact larynx [13].

Study by Vermorken et al., where TPF induction regimen i.e addition of docetaxel to Cisplatin and 5-FU was compared with PF followed by radiotherapy alone in patients with unresectable tumours demonstrated TPF improved a better survival rate with an acceptable toxicity profile when compared to PF. Recent similar studies by Schrijvers et al., Hadad et al., have showed the superior response of induction chemotherapy with taxol group of chemotherapeutic agent (docetaxel/paclitaxel) along with Cisplatin and 5 fluorouracil in controlling the tumour progression, prolonged survival rate, increased disease free period; our study was confined only to conventional standard chemotherapeutic agents involving Cisplatin and 5-Fluorouracil because of financial instability of the patients and lack of availability of taxel compounds in the government hospital [6,14,15].

TOXICITY

The overall major toxicity observed in our study was nonspecific adverse effects including diarrhea, constipation, myalgia, loss of taste, excessive sweating and weight loss constituting 50% among the cases. The usage of pre-medication drugs: Inj. Dexamethasone of 4-8mg; Inj. Rantac 50mg; Inj. Emeset 8mg in 100 ml NS over ½ hr may have resulted in fewer incidences of nausea and vomiting. The specific significant side effect noted in females was anaemia (p=0.00) and thrombocytopenia (p=0.021) and in males it was leucopenia. Other toxic effects likes asthenia was predominant in both the groups. Despite of use of premedication agent's nausea and vomiting was noted in 20.5% of patients. Based on the common toxicity criteria manual, 47.6% of patients developed moderate and 42.1% developed mild adverse reactions related to induction chemotherapeutic agents. Only 9.5% of patients experienced severe and undesirable adverse reactions necessitating the requirement of active treatment. Neither severe nor death related adverse event was seen during the course of chemotherapy. This may indicate the dose related toxicity of Cisplatin and 5-FU is negligible if the patient's general condition is adequate for starting chemotherapy along with necessary use of premedication agents.

CONCLUSION

With the use of cisplatin and 5-FU as induction chemotherapy agents in advanced and inoperable squamous cell carcinoma of head and neck, a distinct benefit was seen in stabilizing the tumour from progression. But achieving a significant complete response to the same is of faint possibility. An alternate multidrug regimen or multimodality treatment would be ideal to gain the optimum results from induction agents. Toxicity related to chemotherapy usually is transient at therapeutic doses, and can be controlled by adequate prophylactic measures.

REFERENCES

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90.

[2] Pacagnella A, Orlando A, Marchiori C, et al. A phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study of the Gruppo di Studio sui Tumouri della Testa e del Collo. *J Natl Cancer Inst*. 1994;86:265–72.

[3] Merlano M, Benasso M, Corvo R, et al. Five year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in the treatment of unresectable squamous cell carcinoma of the head and neck. *J Natl Cancer Inst*. 1996;88:583-89.

[4] Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta analyses of updated individual data. *Lancet*. 2000;355:949-55.

[5] Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. 2007;357:1705–15.

[6] Vermorken JB, Remenar E, van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med*. 2007;357:1695-704.

[7] Karnofsky DA Burchenal JH. (1949). "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. *Columbia Univ Press*. Page 196.

[8] American Joint Committee on Cancer. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.

[9] Eisenhauer EA, Therasseb P, Bogaerts J, Schwartzd LH, Sargent D. New response evaluation criteria in solid tumours: Revised RECIST guideline. *European Journal of Cancer* 2009;45:228-47.

[10] Clayman GL, Lipman SM, Laramore GE, Ki Hong W. Head and neck neoplasms. In Holland JF, Kufe DW, Pollock RE et al. (eds): Holland–Frei Cancer Medicine, 5th edition. Philadelphia, PA: BC Decker 2000; 1173–22.

[11] Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C, et al. Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation. *J Natl Cancer Inst*. 2009;101:498-506.

[12] Jacobs C, Goffinet DR, Goffinet I, Kohler M, Fee W. Chemotherapy as a substitute for surgery in the treatment of advanced resectable head and neck cancer. *Cancer*. 1987;60:1178-83.

[13] Forastiere AA, Maor M, Weber RS, et al. Long-term results of Intergroup RTOG 91-11: a phase III trial to preserve the larynx - induction Cisplatin/5-FU and radiation therapy versus concurrent Cisplatin and radiation therapy versus radiation therapy. *J Clin Oncol*. 2006;24 Suppl: 284s.

[14] Schrijvers D, Van Herpen C, Kerger J, et al. Docetaxel, Cisplatin, and 5-Fluorouracil in patients with locally advanced unresectable head and neck cancer: a phase I-II feasibility study. *Ann Oncol*. 2004;15:638-45.
[15] Haddad R, Tishler R, Wirth L, Norris CM, Goguen L, Sullivan C, et al. Rate of pathologic complete responses to docetaxel, cisplatin, and fluorouracil induction chemotherapy in patients with squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg.* 2006; 132:678-81.

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