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Role of Granulocyte Colony Stimulating Factor Administered During Weekends in Reducing Oral Mucositis of Chemoradiation in Head and Neck Cancers

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Abstract

Introduction: Cancer is a leading cause of morbidity and mortality worldwide. The head and neck cancers form the seventh most common cancer and a major health problem worldwide. *Aims:* To compare and contrast the role of Granulocyte Colony Stimulating Factor (GCSF) given during weekends in reducing the incidence of oral mucositis in Head and Neck cancer patients receiving concurrent chemoradiotherapy with weekly cisplatin. *Materials and methods:* This was a prospective two arm comparative study done in the Department of Radiotherapy, Total 70 patients of locally advanced head and neck squamous cell cancers who underwent treatment from the Department of Radiation Oncology from January 2015 to September 2016 were enrolled in the study. *Results:* Onset of mucositis in control group patients at 8^{th} fraction & 10^{th} fraction were 20% and 51% respectively. Majority of patients (51%) in control group developed mucositis in 10^{th} fraction whereas majority of patients (63%) in study group developed mucositis in 13^{th} fraction. This difference in the onset of mucositis was statistically significant with chi-square *p*-value of 0.000. This clearly indicates GCSF postpones the onset of radiation induced mucositis. *Conclusion:* Usefulness of G-CSF in reducing the onset as well as severity of chemoradiation induced mucositis in patients receiving radiation to head and neck cancers.

Keywords: Granulocyte Colony Stimulating Factor; Oral Mucositis; Concurrent chemoradiotherapy.

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Introduction

Head and neck cancers are common in several regions of the world where the prevalence of tobacco and alcohol consumption is high. Of the 1,41,00,000 total cancer cases diagnosed all over the world in 2012. In India, 6.5% of the total population is represented by older persons (60 years and above). The burden of cancer in India is on the rise with the control of infectious diseases and increased longevity of the growing population.[1]

Radiotherapy being a local treatment leads to mucositis in the irradiated area while chemotherapy adds to the local mucositis as well as entire mucosa of the Gastrointestinal Tract. Many patients who are receiving chemotherapy become immunocompromised. In these neutropenic patients oral mucositis poses a significant risk for local and systemic infections. Oral mucositis is caused by a multi-step biological process, which will occur in 30 to 40% of patients receiving chemotherapy, 60% of patients receiving radiation therapy and 92% of patients receiving

both chemotherapy and radiation therapy.[2] The incidence of grade 3 or higher mucositis is about 34% of patients who receives conventional radiotherapy (RT) which increases to 56% in patients receiving altered fractionation radiotherapy. The addition of chemotherapy also increases the risk of severe mucositis, and intensity varies with chemotherapeutic regimen and dose. Patient related factors, may also contribute to development of mucositis, like age older than 65 years, poor oral hygiene practices.

Currently there is no standard treatment for oral mucositis in HNSCC (Squamous cell carcinoma of the head and neck) The Food and Drug Administration (FDA) has no approved intervention for prevention of radiation induced mucositis.[3] Current management of oral mucositis is limited to symptom control including pain relief and maintenance of good oral hygiene. One of the interventions for the management of radiation induced mucositis is Granulocyte-colony stimulating factor (G-CSF or GCSF).[4,5] It is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. G-CSF also stimulates the survival, proliferation, differentiation, and function of neutrophil precursors and mature neutrophils there by promotes wound healing. The present study was designed to know the effect of subcutaneous Granulocyte colony stimulating factor on the onset and severity of Radiation Induced oral Mucositis in Head and Neck Cancer patients receiving concurrent Chemo radiotherapy.

Aims

To compare and contrast the role of Granulocyte Colony Stimulating Factor (GCSF) given during weekends in reducing the incidence of oral mucositis in Head and Neck cancer patients receiving concurrent chemoradiotherapy with weekly cisplatin.

Materials and Methods

This was a prospective two arm comparative study done in the Department of Radiotherapy, Oncology and Regional Cancer Center. Following ethics committee approval 70 patients of locally head and neck squamous cell cancers who underwent treatment from the Department of Radiation Oncology from January 2015 to September 2016 were enrolled in the study.

Inclusion Criteria

Age between 20 and 65 years, Patients presenting with a locally advanced stage, non metastatic and histopathologically proven head and neck squamous cell carcinoma arising from oral cavity, oropharynx, which have to be treated primarily by concurrent chemo radiotherapy with weekly cisplatin, ECOG performance status of 0–2.

Exclusion Criteria

Performance status ECOG PS >2, Tumors with histology other than squamous cell carcinoma. Patients who had prior underwent surgery or neoadjuvant chemotherapy for the tumour, abnormal haematological or renal parameters, co-morbid conditions which would interfere in treatment decisions, Evidence of distant metastasis, Hypersensitivity to G-CSF.

Initial evaluation and workup

A standardized data collection proforma was used for the study which incorporated thorough history and physical examination including appropriate endoscopic assessment if indicated. All the cases underwent biopsy or FNAC (Fine Needle Aspiration Cytology) for confirmation of malignancy. Complete blood count, renal function tests, liver function tests, Chest X-Ray PA view, Ultrasound abdomen, Computer tomography scan of head and neck site for location and extent of the disease, Dental evaluation as a part of pre-Ratiotherapydental prophylaxis after assessing the clinical stage and deciding the definitive treatment and assessment of ECOG Performance score was done.

A total of 70 patients of locally advanced head and neck squamous cell carcinoma were randomised into:

ARM A: consisting of 35 patients receiving Radical Radiotherapy of 66Gy, 2 Gy/fraction, 5 fraction per week and concurrent chemotherapy with Inj. Cisplatin 40 mg/m^2 given every week during radiotherapy, 75 mcg of subcutaneous G-CSF given on weekends (Saturday, Sunday).

ARM B: consisting of 35 patients receiving Radical Radiotherapy of 66 Gy, 2 Gy/ fraction, 5 fractions per week and concurrent chemotherapy with Inj. Cisplatin 40 mg/m^2 given every week during radiotherapy without G-CSF.

Phase I: 44 Gy/22 fractions, 5 fractions per week to volume comprising the gross disease with extension and nodal areas at risk.

Phase II: 22 Gy/11 fraction, 5 fraction per week to boost volume, sparing the spinal cord which includes the gross tumor volume with margin. The radiation dose delivered to the lower neck portal was 5000 cGy in 25 fractions. Posterior electron boost field was added who had involved level V nodes or in patients with large nodes that could not be covered in off-cord reduced fields. The plans were evaluated using Dose Volume Histogram analysis and the best plan was selected for treatment, which was transferred to Linear accelerator for implementation. Set up verification was done with the electronic portal imaging device. Radiotherapy was delivered by VARIAN linear accelerator (LINAC) using 6MV X-rays. Patients in both arms received concurrent chemotherapy with cisplatin 40 mg/ m^2 given weekly with radiotherapy.

Chemotherapy Protocol

The drug CISPLATIN was used as a single agent concurrently with the radiotherapy. The dosage used was 40mg per meter square weekly for 5–7 cycles. The patient was started on chemotherapy after adequate hydration and pre medication. CISPLATIN was administered with normal saline and given over 2 to 3 hrs IV infusion. It is followed by radiotherapy within 1 hr after completion of infusion. Myelosuppression and renal toxicity is evaluated by doing complete heamogram, blood urea and serum creatinine weekly.

Study Protocol

At the end of first week of radiation therapy, patients in study group were administered with a dose of 75 μg/day (0.25 ml) of G-CSF subcutaneously on Saturday & Sunday mornings throughout the treatment period (6–7 weekends), and only radiation therapy in the remaining week days(Monday-Friday). A time gap of 24 hrs was maintained between G-CSF and RT, 24–48 hours gap was maintained between G-CSF and chemotherapy. Total WBC count was measured before and after administration of G-CSF. Control group patients were given G-CSF only therapeutically at Grade-3 mucositis with neutropenia. Remaining treatment & supportive care was same for both the groups. Myelosuppression and renal toxicity are evaluated by doing complete heamogram, blood urea and serum creatinine weekly. From the second week of treatment, all patients in both the groups were assessed every week for the onset and severity of oral mucositis according to RTOG grading system until two weeks after the completion of radiation treatment.

General management, advice and precautions

Adequate hydration was maintained with the help of oral and i.v. fluids. Patients were counselled about easy and cost effective ways of maintaining protein-calorie intake. All patients were encouraged for nasogastric tube feeding. Active support of the Palliative care team was sought in order to ensure a holistic approach. All attempts were made to minimize treatment delays in RT even when patient was unable to take chemotherapy due to toxicities. Necessary gap corrections were done for RT delays. Antiemetics were given on the day and following four days of chemotherapy. Importance and the methods to maintain oral hygiene, tracheostomy care(when indicated) was explained to the patients.

Follow up

All the patients were followed up initially on the date of completion of treatment, one week after completion of treatment and two weeks and six weeks after completion of treatment.

All Patients were assessed twice a week (3 & 5 in 1st week, 8# & 10# in 2nd week, 13# &15# in 3rd week,18# & 20# in 4th week, 22# & 25# in 5th week, 28# & 30# in 6th week, 33# in 7th week), 1st week post RT, 2nd week post RT for tumor response and complication development. Development of mucositis was assessed using clinical examination under good light. RTOG (Radiation Therapy Oncology Group) grading system was utilized to grade the mucositis.

RTOG Grading System

Grade 0: No change

Grade 1: Mucosal erythema

Grade 2: Studded mucositis / Patchy mucositis

Grade 3: Confluent mucositis not requiring intervention

Grade 4: Ulceration, necessitates for treatment break.

Statistical Analysis

At the end of the study, incidence of chemo radiation induced mucositis, duration of treatment & number of break outs of both groups were compared, depicting the significance of G-CSF. Outcomes of the study were measured by the Standard Package Statistical Software (SPSS version 17.0), and Microsoft word and Excel have been used to generate graphs, tables etc.

Results

Patients were in the age group of 23–60 years in study group whereas 25–64 in control group. The mean age of patients in study group was 42.65 with standard deviation of 10.22. The mean age of patients in control group was 43.85 with standard deviation of 9.67. The following table shows the age range and number of patients in each group. 12 out of 35 patients were females in study group whereas 15 out of 35 were females in control group (Table 1).

Table 1: Demographic details in present study

Patients Characteristics		Number of patients (*N*=70)	Percentage	Number of patients	Percentage
Sex	M	23	65.7	20	57.1
	F	12	34.3	15	42.9
Age (yrs)	Median	55.5		55.5	
	Mean	42.65		43.85	
	Range	23–60		25–64	
Primary site					
	Ca.Tongue	13	37	11	31
	Ca. Buccal mucosa	7	20	4	11
	Ca. Alveolus	5	14	3	8.5
	Ca. Floor of mouth	5	14	3	8.5
	Ca. Hard palalte	1	3	3	8.5
	Ca. RMT	0		3	8.5
	Ca. oropharynx	4	11	12	34
Histological grading					
	well differentiated	22	63	23	66
	moderately differentiated	5	14	7	20
	poorly differentiated	8	23	5	14
T-stage					
	T3	13	37	12	34
	T4a	21	60	23	66
	T4b	1	3	0	
N-stage					
	N0	0	0	2	6
	N1	10	29	10	29
	N2	24	68	23	55
	N3	1	3	0	0
AJCC staging					
	III	5	14	4	11
	IV a	28	80	31	88
	IV b	**23-60**	**6**	**0**	**20**

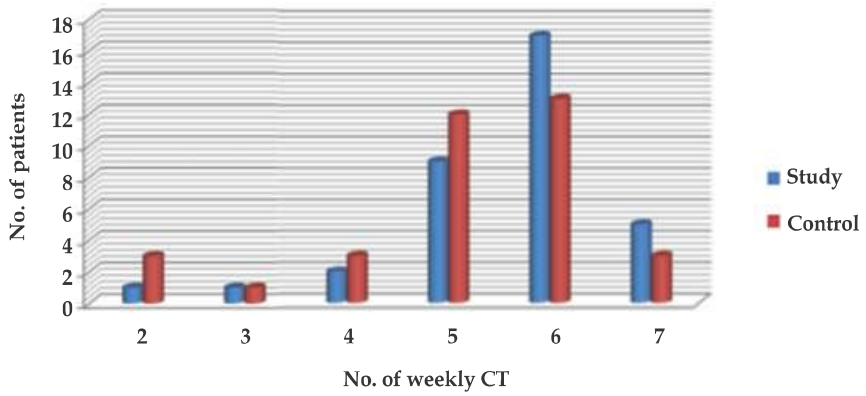

Fig. 1: Distribution of cases according to total number of weekly inj.cisplatin received

In study group, the most common sub site of carcinoma of oralcavity was tongue (*n*=13) constituting 37% of all the cases (Fig. 1).

The patients were assessed regularly twice a week for the onset of mucositis and severity of mucositis according to RTOG mucositis grading system. The Pattern of mucositis in study group and control group were as follows:

Two (5.7%) patients in study group and 7 (20%) patients in control group developed grade1 mucositis at 8th fraction. 5 (14%) patients in study group and 18 (51%) patients in control group developed Grade 1 mucositis at 10th fraction. 22 (62.9%) patients in study group and 9 (25.7%) in control group developed Grade 1 mucositis at 13th fraction. 5 (14%) patients in study group and 1 (2.9%) patient in control group developed Grade 1 mucositis at 15th fraction and 1 patient developed at 18th fraction in study group (Table 2).

Assessment of mucositis 1 week after radiotherapy 31 (93.9.5%) patients were without mucositis, only 2 (6.1%) were with Grade 1 mucositis in study group at the end of 1 week after radiotherapy. 24 (77.4%) patients were without mucositis, 7 (22.6%) patients were with Grade 1 mucositis in control group (Fig. 2).

Assessment of mucositis 2 weeks after radiotherapy: At the end of 2 weeks after radiotherapy oral mucositis is completely absent in patients of both study and control groups

Table 2: Onset of mucositis in study group and control group patients

Fraction	Study		Control		Total		df	*p*-value
	n	%	*n*	%	n	%		
Eight	2	5.7	7	20	9	12.9		
Ten	5	14	18	51	23	32.9		
Thirteen	22	62.9	9	25.7	31	44.3	4	0.001
Fifteen	5	14	1	2.9	6	8.6		
Eighteen	1	2.9	0	0	1	1.4		

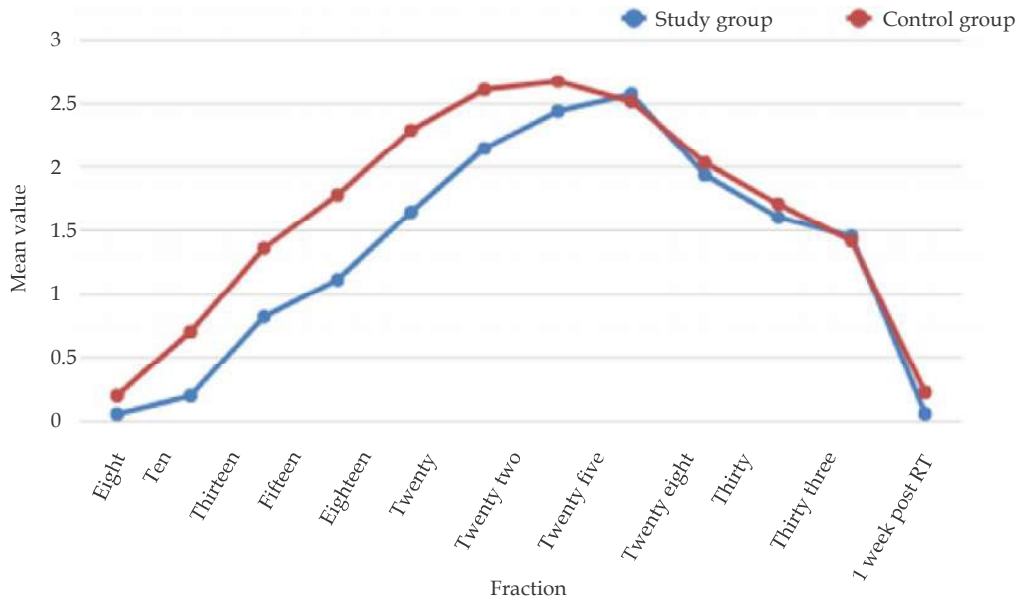

Fig. 2: Study and control Groups mean mucositis score.

In study group out of 35 patients, 24 (73%) patients completed treatment without any breaks, 9 (27%) patients completed with unscheduled breaks in the treatment period. In control group out of 35 patients 10 (32.25%) completed treatment within scheduled time, 21 (67.74%) patients completed treatment with breaks. Two patients among the study group and 4 among the control group have absconded. The observed mean total treatment duration of study group was 47.12 days whereas for the control group was 49.29 days. Incidence of Grade-3 mucositis was observed in 21/35 patients

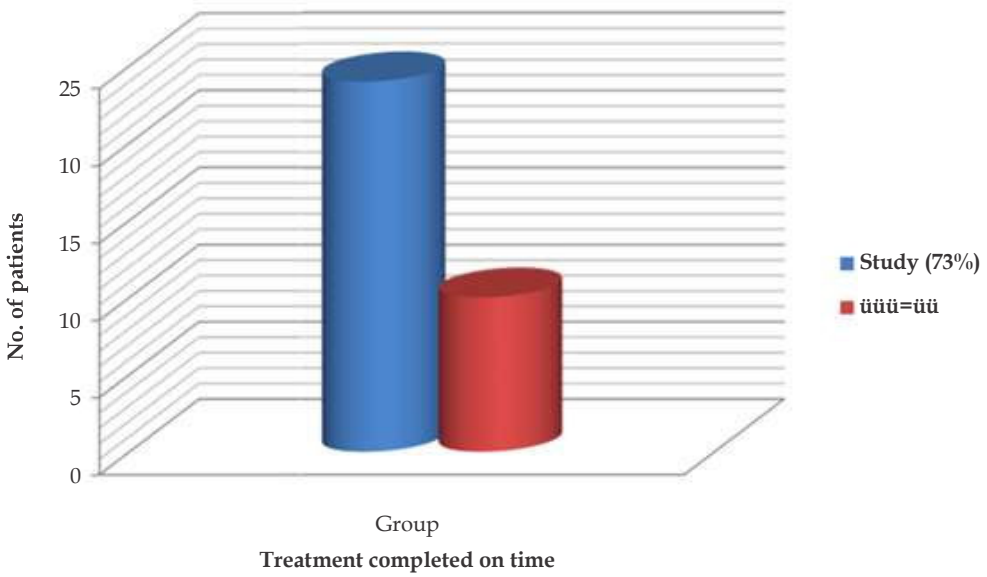

Fig. 3: Mean mucositis score for study group and control group.

in study group and among them only 9 patients had treatment breaks. Whereas in control group, 31/35 patients got Grade-3 mucositis out of whom 21 patients had treatment breaks (Fig. 3).

Discussion

The basis of management of radiation mucositis is targeted to its four defined pathogeneses are most important is to check basal cell layer growth by modifying transforming growth factor β^3. The second mechanism is stimulation of epithelization, thereby encouraging rapid recovery of cell loss. Third is the chemical protection of mucosa using the Amino-Thiol group of compounds like amifostine. Last but not least is the physical protection of oral mucosa by shield use, conformal therapy or intensity modulated radiotherapy. Local antibiotics in the form of lozenges have been tried with the hope of preventing bacterial colonization and reducing inflammation of damaged mucosa.

Low energy He/Ni laser treatment may promote the proliferation of mucosal cells, and wound healing has been tried for the treatment of chemotherapy/radiotherapy induced mucositis. The above treatments are cumbersome and produce no consistent results. Moreover there is no standard treatment for radiation induced mucositis. In this study, to know the effectiveness of GCSF on radiation induced mucositis, 75 mcg of filgrastim was used as subcutaneous injection given over weekends i.e., on Saturday and Sunday mornings during the entire course of treatment starting from the first weekend. Oral mucosal defense mechanism is enhanced by the local accumulation of activated neutrophils subsequent to systemic administration of granulocyte colony-stimulating factor (G-CSF). Patients were allocated to study group and control group based on inclusion and exclusion criteria. Filgrastim was given only to study group patients, and standard care to both group patients as per the study design. According to the study design patients were assessed two times a week of 5/1 wk schedule of radiation treatment. The onset of mucositis and the severity of mucositis were noted at every assessment.

Age and sex of patients

In this study the age group of patients varied from 23–60 years in study group and 25–64 years in control group. The mean age of patients in study group was 42.65 with standard deviation of 10.22. The mean age of patients in control group was 43.85 with standard deviation of 9.67. According to Dodd younger patients of age less than 20 years are more susceptible for oral mucositis due to more rapid epithelial mitotic rate or the presence of more epidermal growth factor receptors in the epithelium at the early age.[2] On the other hand, the physiologic decline in renal function associated with aging may result in higher incidence of oral mucositis in older patients of age more than 65 years. Though the mean age of study group is less than the control group, there was no statistically significant difference between two groups. 12 patients out of 35 were females in study group where as 15 out of 35 patients were females in control group.

Mascarin *et al*.[6] conducted a similar study on 26 patients of head and neck cancer presented with advanced stage of disease (Stage III and IV). In our study also, almost more than three-fourth of the patients in study arm presented with an advanced stage of the disease-IVa (non metastatic, *n*=28, 80%), Stage IVb (*n*=2,6%), the remaining patients are of Stage III (*n*=5, 14%). In control group also 89% are of Stage IVa (*n*=31), remaining are of Stage III (*n*=4, 11%). In study arm, twenty one patients (60%) had T4a stage disease at the time of presentation. About 37% (*n*=13) of the patients presented with T3 disease and 3% had T4b disease (*n*=1). In control arm 66% (*n*=23) of the patients were of T4a, 34% are stage T3 (*n*=12). In study arm 29% of the patients (*n*=10) had N1 nodal disease. Patients with N2 and N3 nodal stage were 68% (*n*=24) and 3%(*n*=1) respectively. In control arm 66% (23) of the patients had N2, 28% were of N1 (*n*=10), and two patients (6%) had N0 nodal status. Also, these results were comparable to a study by Vokes EE *et al*.[7] in the past where most of the patients presented with advanced head and neck cancer. In study group, the most common sub site of carcinoma of oral cavity was tongue (*n*=13) constituting 37% of all the cases, Seven patients have tumor in the buccal mucosa region (20%), followed by alveolus(14%), floor of mouth(14%), hard palate(3%). while only four (12%) patients have disease in the oropharynx. Where as in control group tongue (*n*=11,31%), buccal mucosa (*n*=4,11%), alveolus, FOM, hard palate, retromolar trigone (*n*=3, 8.5%), & oropharynx (*n*=8,23%). In study group 63% percentage of the cases (*n*=22) have well differentiated squamous cell carcinoma. Poorly differentiated histology constituted 23% (*n*=8), moderately differentiated were 14%% (*n*=5) and in control group well differentiated constitutes 66% (*n*=23), poorly differentiated 20% (*n*=7) and moderately differentiated were 14% (*n*=5).

Onset of radiation induced mucositis

In this study, the patients were assessed for onset of mucositis during radiation treatment twice a week as per the study design. No patients developed RIM at 3rd, 5th fraction assessment either in study group or control group. 2 (5.7%) patient in study group and 7 (20%) patients in control group developed Grade-1 mucositis at 8th fraction. 5 (14%) patients in study group and 18 (51.4%) patients in control group developed grade 1 mucositis at 10th fraction. 22 (62.9%) patients in study group and 9 (25.7%) patients in control group developed mucositis at 13th fraction. 5 (14%) patients in study group and 1 (2.9%) patient in control group developed mucositis at 15th fraction. 1 (2.9%) patient in study group and 0 (0%) in control group developed mucositis at 18th fraction.

These findings infer that the onset of mucositis at 8th (20%) & 10th (51.4%) fraction constituted 71.4% of control group patients whereas the onset of mucositis at 8th (5.7%) & 10th (14%) in study group patients constituted 19.7% of patients of study group. Majority of patients (51.4%) in control group developed mucositis at 10th fraction whereas majority of patients (62.9%) in study group developed mucositis at 13th fraction. This difference in the onset of mucositis was statistically significant with *p*-value of 0.05. In the present study, the results have shown that the onset of mucositis for majority of study group patients was at 13th fraction whereas for control group patients was at 10th fraction.

Severity of mucositis

In this study mucositis was assessed twice a week till the end of radiation treatment. Thus patients were assessed at 3rd, 5th, 8th, 10th, 13th, 15th, 18th, 20th, 22nd, 25th, 28th, 30th and 33rd fractions, 1 week and 2 week post RT.

Pattern of mucositis

The pattern of mucositis showed that all patients either in study group or control group developed mucositis. The majority patients in study group developed mucositis around 10th & 13th fraction (76.9%) and severity was increased as the fractions were increased and towards the end of the radiation treatment severity was decreased. The same kind of pattern was observed in control group also, except that the onset of mucositis in majority of patients was observed around 8th & 10th fraction (71.4%).

Average Mean Oral Mucositis Scores

The mean mucositis score for study group was 1.33 whereas it was 1.62 for control group. This clearly showed the control group patients were with higher grades of mucositis than study group patients. No patient either in study group or control group developed mucositis at Third and Fifth Fraction.

After 8th fraction, 1 patient in control group left the treatment. The difference between two groups was statistically significant with *p*-value of 0.00 which is <0.05. It shows that filgrastim is effective in delaying the onset of mucositis. After 10th fraction, 1 patient in study group and 1 patient in control group left the treatment. The difference between two groups was statistically significant with *p*-value of 0.00. It indicates that the filgrastim is effective in decreasing the severity of mucositis.

After 13th fraction, 1 patient in control group left the treatment. There was a statistically significant difference between two groups with *p*-value of 0.00. It indicates that the filgrastim is effective in reducing the severity of mucositis. After 15th fraction, 1 patient in control group left the treatment. The difference between two groups was statistically significant with *p*-value of 0.00. It clearly shows that the filgrastim decreases the severity of mucositis.

Assessment at Twentieth Fraction difference of borderline significance was observed for the reduction of maximum severity of oral mucositis between G-CSF vs control group (*p*=0.08).

After 22nd fraction, 1 patient in study group left the treatment. The difference between two groups was statistically not significant with *p*-value of 0.802. Assessment at Twenty eighth Fraction the difference between two groups was statistically not significant with *p*-value of 0.153.

Assessment at Thirtieth Fraction difference between two groups was statistically not significant with *p*-value of 0.514. Assessment at Thirty third fraction difference between two groups was statistically not significant with *p*-value of 0.806. In view of severity, *p*-values at 25#, 28#, 30#, 33# fractions may not be significant, but the breaks taken and thus the treatment time durations for the patients in control group at each particular fraction is more than that of study group. In study group out of 35 patients, 22 (66.6%) patients completed treatment without any breaks, 11 (33.3%) patients completed with unscheduled breaks in the range of 3–7 days in the treatment period. Whereas in control group out of 35 patients 10 (32.25%) completed treatment within scheduled time, 21 (67.74%) patients completed treatment with breaks in the range of 2–12 days in the treatment period. Assessment at 1 week post RT difference between two groups was statistically significant with *p*-value of 0.05.

Assessment at 2 week post RT

No patients either in study group or control group were having mucositis. The results of this study were consistent with the following clinical trials investigating the effect of filgrastim on oral mucositis, using a similar study protocol. Schneider *et al*. conducted a study[8] to determine the effect of filgrastim in reducing the incidence and severity of oral/oropharyngeal mucositis in patients receiving external beam irradiation for head and neck malignancies. Patients were randomized to receive subcutaneous injections of either filgrastim or placebo beginning on day 1 of radiation and continuing daily throughout treatment. Study medication was titrated to keep the neutrophil count between 10 × 10 (9) and 30 × 10 (9)/l. The left and right buccal mucosa, hard palate, and posterior pharyngeal wall were scored weekly, by a blinded evaluator using two different scales, and the most severe score per week was used in data analysis. Fourteen of a planned 54 patients were randomized (8 filgrastim, 6 placebo), and were evaluable for a planned interim analysis. No statistically significant between-group differences were seen in mean worst scores across time using repeated measures analysis of variance (Hickey, p = 0.231; WHO, p = 0.288). At almost all time points, however, the worst mean scores were lower in patients treated with filgrastim compared with those in patients treated with placebo, and the number of severe (i.e., Grade 3) mucositis scores was significantly lower in the filgrastim-treated group. Filgrastim may decrease the severity of radiation-induced oral/ oropharyngeal mucositis. Our study results were consistent with the above study, and mucositis assessment at later fractions was statistically not significant but Grade-3 mucositis score was significantly lower in study group. Martín Tejedor *et al* in their non-randomized study[9] evaluated the feasibility and efficacy of filgrastim (recombinant methionyl human granulocyte colony-stimulating factor, r-metHuG-CSF) to prevent mucositis induced by accelerated hyperfractionated radiotherapy (1.6 Gy b.i.d., total dose 67.2 Gy in six weeks with a two-week split) and concomitant chemotherapy (cisplatin, 20 mg/m^2/day, days 1–5 by continuous intravenous infusion) in patients with laryngeal carcinoma. Filgrastim 300 microg/day was administered on days 1, 3, and 5 in weeks 2–6 of radiotherapy, after the second fraction. Twenty patients (three Stage II, six Stage III, and eleven Stage IV, according to AJCC) were enrolled in the trial. Oral mucosal toxicity was Grade 2 in nine patients (45%), Grade 3 in eight (40%), and Grade 4 in three (15%). Severe hematological toxicity (WHO criteria) was uncommon. Nineteen patients (95%) completed the treatment in the planned time. Overall survival was 55% at three years. The administration of filgrastim with this regimen was feasible, and it appeared to reduce the severity and duration of mucositis induced by the combined treatment. Severity and duration of mucositis was less in patients among our study group, similar to the above study. In study group, incidence of Grade-3 mucositis is observed in 21/35 patients and 73% patients completed treatment without any breaks. Whereas in control group, 31/35 patients got Grade-3 mucositis, and only 32.25% of patients

completed treatment without any breaks. Mascarin *et al*. (103) investigated the effect of granulocyte colony-stimulating factor (G-CSF) administration on radiotherapy (RT)-induced oral mucositis in 26 consecutive patients with head and neck neoplasms, Stages III and IV, treated with hyperfractionated RT. The first 13 patients were treated with RT alone and the remainder with RT + G-CSF. The two groups of patients were similar in age, sex, PS, primary site, stage, RT schedule and RT volume. Daily mucositis, median mucositis score, day of highest mucositis, requirement of parenteral nutrition, weight loss, treatment break, number of days of RT interruption were analyzed during RT treatment. No statistically significant differences were found between the two groups except for the number of patients who interrupted the treatment: 9/13 patients (69%) in the RT alone group versus 3/13 (23%) in the RT + G-CSF group ($p < 0.05$). Their observations indicate that G-CSF did not appear to have influenced the objective mucositis although it reduced the number of treatment breaks. Also in consideration of the cost of G-CSF, they mentioned that its prophylactic administration should be reserved only for patients at high risk of RT interruption. In our study, patients were chosen on similar characteristics like Stages III and IV HNSCC. Mucositis score assessment was done twice in a week and mean mucositis score, total treatment duration, number of treatment breaks were calculated and analysed. Our results also showed that number of treatment breaks was less in study group [21/31 patients (68%) in without GCSF group versus 9/33 (27%) in GCSF group], in addition our study analyses showed that G-CSF had effect on onset of mucositis ($p < 0.05$). Vokes *et al*.[5] observed the effects of G-CSF in ameliorating the dose limiting toxicities like mucositis and myelosuppression in a study conducted on patients with locally advanced head and neck cancer using intensified concomitant chemoradiotherapy [cisplatin, fluorouracil (5-FU), hydroxyurea (HU), and concomitant radiotherapy]. Chemoradiotherapy consisted of 1.8 to 2.0 Gy on days 1 to 5 with simultaneous infusional 5-FU at 800 mg/m^2/d and HU administered every 12 hours for 11 doses at escalating doses. Cisplatin was administered at 100 mg/m^2 during every other cycle. Cycles were repeated every 14 days until completion of radiotherapy. G-CSF was added on days 6 to 13 at 5 micrograms/kg/d. No increase in acute toxicities like mucositis was seen among G-CSF group and thus total treatment duration was deceased and there by good loco regional control. In our study, patients receiving G-CSF showed decrease in severity and duration of mucositis and thereby total treatment duration.

Karthaus *et al*.[10] performed a prospective randomised placebo-controlled trial using topical oral r-metHuG-CSF (filgrastim) in high-grade lymphoma patients treated according to the B-NHL protocol, which contains high-dose methotrexate and causes severe oral mucositis (WHO Grades I-IV) in >50% of patients. Mucosal erythema and ulceration were recorded among the patients who received 32 chemotherapy cycles. All patients assessed their oral pain and impact on swallowing daily, using a subjective scale from no to maximal discomfort.[1–10] In addition, oral mucositis was assessed according to the WHO score. Filgrastim was administered in 16 cycles as a viscous mouthrinse (carboxymethylcellulose 2%, oleum citrii) 4 × 120 microg/day from days 10 to 16. Sixteen cycles were given to control patients, of these 14 with placebo, and another two cycles with no treatment. Severe mucositis (WHO Grade III/IV) was documented in 21 of 32 cycles (65.5%). A difference of borderline significance was observed for the reduction of maximum severity of oral mucositis between G-CSF vs placebo (p=0.058), with a reduction of WHO grade IV of 50% (four G-CSF vs eight control). The number of days in hospital was reduced significantly in the G-CSF group (p=0.02). In their conclusion, topical oral G-CSF mouthrinses may be beneficial to reduce oral mucositis. In our study we gave G-CSF subcutaneously and observed a similar result of decrease in severity of mucositis. In studies by Viswanath *et al*.[11], and also in a review study by Plevová P[12] mentioned that effects of G-CSF are promising in prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis.

Conclusion

Concludes that filgrastim was effective in reducing the severity of radiation induced mucositis. In contrary to control group, most of the patients in study group completed the treatment on time without unscheduled breaks. The mean mucositis score for study group was 1.33 whereas it was 1.62 for control group. This clearly showed the control group patients were with higher grades of mucositis than study group patients.

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