Original research article

ORAL MUCOSITIS IN PATIENTS OF HEAD AND NECK CANCERS TREATED WITH CHEMORADIOTHERAPY: ASSOCIATED FACTORS AND TREATMENT OUTCOME

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Abstract

Introduction: Oral Mucositis develops in nearly all patients receiving radiation therapy for head and neck cancers. Number of risk factors has been reported to influence the frequency and severity of Mucositis. The goal of the present study is to evaluate some of the patient and treatment related factors which make impact on oral mucositis and also to evaluate the impact of oral Mucositis on treatment outcome.

Material and Methods: Fifty patients were included in this study from July 2014 to June 2016. All the patients were treated with concurrent radiotherapy (70 Gy in 35 fractions in 7 weeks) and chemotherapy (Cisplatin 35 mg/m2 weekly). Clinical Response Assessment was done as per RTOG Grading and Radiation toxicity was assessed by RTOG Acute & Late Morbidity Scoring criteria. Statistical analysis was done using Chi Square test and Fischer Test.

Results: In a patient population of fifty, the intensity of oral Mucositis was correlated with various patient and treatment related factors. Patient related factors- body mass index ≤ 18.5 and patients taking tobacco had a higher incidence of Grade III/IV Mucositis ($p<0.00$ & $p=0.04$ respectively). Other factors like age, gender, stage, site of disease and co morbidities did not show statistical difference in Grade III/IV oral Mucositis. None of the treatment related factors- total dose of Cisplatin, number of chemotherapy cycles and radiation dose showed statistical difference in the occurrence of oral Mucositis.

Conclusion: Severe oral Mucositis leads to additional supportive care & even hospitalization. Targeted interventions need to be developed to reduce the incidence of oral Mucositis.

Keywords: oral mucositis, head and neck cancers, chemoradiation, prognostic factors

INTRODUCTION

Oral mucositis develops in nearly all patients receiving radiation therapy for head and neck cancer. Severe mucositis has a major impact on patient's daily functioning, wellbeing and quality of life. It can compromise a patient's ability to tolerate planned therapy resulting in missed doses or dose reductions.[1] Moreover it can negatively affect other health outcomes as well increasing the risk of opportunistic infections and mortality due to sepsis. It represents a major non hematologic complication of cytotoxic chemotherapy and radiotherapy associated with significant morbidity.

Mucositis manifests as erythema, oedema or ulceration that can be accompanied by alterations ranging from mild burning sensation to large and painful ulcers that worsen patient quality of life and limit basic oral functions such as speech, the swallowing of saliva or eating.[2]

Number of risk factors have been reported to influence the frequency and severity of mucositis. Factors may be related to the patient (age, buccodental health and the nutritional status) or treatment related (concomitant chemotherapy with radiotherapy).[3,4] The frequency of mucositis and its severity are fundamentally dependent upon the type, duration and dose of chemotherapy used.[5]

The goal of the present study is to evaluate some of the patient and treatment related factors associated with oral mucositis and the impact of oral mucositis on treatment outcome.

MATERIALAND METHODS

The present study was done in Department of Radiotherapy at Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, a tertiary health care centre. All the patients included in this study were histologically proven cases of

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head and neck cancer taken from the OPD. Fifty patients were included in this study from July 2014 to June 2016.

The inclusion criteria were age ≥ 18 years; Karnofsky Performance Status (KPS) >70 with normal hemogram, renal function tests, liver function tests and ECHO. The exclusion criteria were patients with prior or synchronous malignancy; distant metastasis present; previously partially treated patients (in terms of surgery, radiotherapy and chemotherapy); patients not fit for cisplatin or paclitaxel based chemptherapy ie, patients with compromised renal or cardiac functions, pregnancy and lactating mothers and patients using high dose NSAIDs.

All the patients underwent pretreatment evaluation by complete history taking, general physical examination, local examination, hemotological and biochemical tests (complete haemogram, renal function tests, liver function tests), radiological investigations (Chest X-ray, USG abdomen, CECT neck) and 2D ECHO.

All the patients were treated with concurrent radiotherapy (70 Gy in 35 fractions in 7 weeks) and chemotherapy (Cisplatin 35 mg/m2 weekly).

Oral mucositis Grading as per Radiation Therapy Oncology Group (RTOG) is Grade 0: No change over baseline; Grade I: Irritation, may experience slight pain ,not requiring analgesic; Grade II: Patchy mucositis that may produce inflammatory serosanguinitis discharge, may experience moderate pain requiring analgesia; Grade III: Confluent, fibrinous mucositis, may include severe pain requiring narcotic; Grade IV: Ulceration, hemorrhage, or necrosis.

Clinical response of the disease was evaluated with WHO Response criteria- Complete response (CR): Disappearance of all known disease determined by two observations not less than 4 weeks apart. Partial response (PR): Sum of products of all lesions decreased by ≥ 50% for at least 4 weeks; no new lesions; no progression of any lesion. Stable disease (SD): Sum of product of lesions decreased by 50% or increased by ≤ 25% in the size of one or more lesions. Progressive disease (PD): a single lesion increased by ≥ 25% or the appearance of new lesions.

Statistical Analysis: Collected data was analyzed using standard statistical methods (Chi square test& Fischer test) and software to calculate level of significance using "P" value. Statistical significance considered with P-value (< 0.05).

RESULTS

In a patient population of fifty, the intensity of oral mucositis was correlated with various patient and treatment related factors (Table 1 & 2).

Table-1: Patient related factors

Characteristics	Grade I & II mucositis n (%)	Grade III & IV mucositis n (%)	P-value
Age (years)			
≤45	06(12%)	8(16%)	0.52
>45	12(24%)	24(48%)	
Gender			
Male	16(32%)	32(64%)	0.12
Female	2(4%)	0(0%)	
BMI			
≤18.5	0(0%)	20(40%)	**0.00**
>18.5	18(36%)	12(24%)	
Personal Habits			
Tobacco & Alcohol Intake	15(30%)	32(64%)	**0.04**
Absent	3(6%)	0(0%)	
Stage			
Early Stage (I&II)	3(6%)	5(10%)	0.92
Late Stage (III&IV)	15(30%)	27(54%)	
Site			
Oral Cavity & Oropharynx	15(30%)	26(52%)	0.85
Hypo pharynx & Larynx	3(6%)	6(12%)	
Co morbidities(HTN,DM,TB)			
Present	3(6%)	6(12%)	0.85
Absent	15(30%)	26(52%)	

HTN: Hypertension; DM: Diabetes Mellitus; TB: Tuberculosis

Table-2: Treatment related factors

Characteristics	Grade I & II mucositis n (%)	Grade III & IV mucositis n (%)	P-value
Dose of Cisplatin (mg)			
≤ 200	9(18%)	20(40%)	0.39
201-350	9(18%)	12(24%)	
Number of cycles (weeks)			
≤ 5	14(28%)	26(52%)	0.76
6 - 7	4(8%)	6(12%)	
Radiation Dose			
≤ 66 Gy	8(16%)	16(32%)	0.66
>66-70 Gy	10(20%)	16(32%)	

Clinical Outcomes: Assessment of oral mucositis on treatment outcome as seen with 52% patients of grade III & IV oral mucositis in this study had complete response and 34% patients of grade I & II oral mucositis had complete response.

The correlation between grade of oral mucositis and treatment response was not significant (p = 0.19).

DISCUSSION

Oral mucositis is a very common complication in patients undergoing concomitant chemo radiation. Several factors are associated with increase in severity of oral mucositis which may lead to compromised treatment in terms of radiotherapy dose and chemotherapy cycles and ultimately leading to failure of planned treatment.

Patient related factors

Age: Patient age may influence the vigour of the immune response directed against the tumour and the patient's ability to tolerate maximal therapy.[6] As per study by Pico et al the impact of age on incidence and severity of mucositis is a contentious issue.[7] In this present study, 24 patients (age>45 years) had grade III & IV oral mucositis and 12 patients (age>45 years) had grade I & II oral mucositis. It has been argued that due to a reduction in renal function associated with the ageing process, older populations may be more at risk. McCarthy et al & Avritscher et al supported the view that reduced renal function increases the toxicity of anti neoplastic medications by altering their pharmacokinetic and pharmacodynamic effects, but it was not identified in any of the 44 multivariate analyses, suggesting that age may not be an independent risk factor for mucositis development.[8,9] Also in present study, age and oral mucositis correlation was not significantly significant (p=0.52).

Gender: It is not considered a significant determinant of oral mucositis in patients with head and neck cancer treated with chemo radiotherapy. In the current study, there were only 2 female patients & none had grade III & IV oral mucositis. Study by Elting et al suggested an association between male gender and higher incidence of mucositis grades III–IV.[10] In our study, male gender was associated with more incidence of oral mucositis but that was statistically not significant (p=0.12) which may be attributed to small sample size.

Body Mass Index (BMI): A lower risk of head and neck cancers mortality has been associated with overweight and obese patients, and there is evidence of an elevated risk of head and neck cancers mortality for lean patients. A statistically significant lower risk of death from cancers of the upper aero-digestive tract was observed in with higher BMI levels ranging from 15 to 25 kg/m^2 and no association was observed for individuals with a higher BMI levels ranging from 25 to 50 kg/m^2.[11] Of the total 50 patients included in this present study, 20 patients (40%) had a BMI of up to 18.5 kg/m^2 and 30 patients (60%) had a BMI above 18.5 kg/m^2. Among them,12 patients (>18.5 kg/m^2) had grade III & IV oral mucositis. and all 20 patients (<18.5 kg/m^2) had grade III & IV oral mucositis. Recently, a statistically significant association has been found between low BMI and grade III-IV mucositis in head and neck cancer patients treated with chemo radiotherapy as per study by Saito et al[12] Also in the present study, correlation between oral mucositis and BMI was statistically significant. (p=0.00).

Tobacco and alcohol intake: Tobacco use has long been recognized as important risk factors for the development of head and neck squamous cell carcinoma.[13] Many authors have speculated that the deleterious impact of smoking may be related to lower levels of natural-killer-cell activity, reduced cell-mediated immunity, and increased blood carboxyhemoglobin concentrations, resulting in tissue hypoxia and increased radio resistance which is related to severity of oral mucositis.[14] Hashibeet al said alcohol abuse is a well-recognized risk factor for oral and oropharyngeal cancer. Alcohol intake is associated with an increased susceptibility of the oral mucosa to acute radiation injury with an increased incidence and severity of mucositis.[15] In this study, 94% patients used to tobacco and alcohol intake. Among them around half (64%) had grade III & IV oral mucositis and 30% patients showed grade I & II oral mucositis. The result of this present study showed intake of tobacco and alcohol associated with more high grade III-IV oral mucositis (p=0.04).

AJCC Stage: Stage III & IV patients associated with higher grade of oral mucositis (grade III & IV) as per studies by Vera-Llonch et al and Van der berg et al.[16,17] In our study, higher AJCC stage was not significant with oral mucositis. The probable reason may be due to preventive measurus and continued conservative treatment given during chemoradiation.

Site of cancer: Site of cancer is also the factor having impact on grade of oral mucositis.[10,18,19] In study by Vera-Llonch,patients with severe oral mucositis were more likely to have nasopharyngeal or oropharyngeal tumors.[17] In our study, twenty six patients of carcinoma of oral cavity and oropharynx developed grade III & IV oral mucositis. The correlation between site of cancer and grade of oral mucositis was not found significant (p=0.85). More number of patients need to be studied for validation of this factor.

Co-morbidities: No specific data are available regarding the impact of comorbidity on mucositis incidence and severity because these patients are frequently excluded from curative treatment programs. The presence of comorbidity had not significant impact (p=0.56) on oral mucositis which is similar to the study by Boje et al.[20]

Treatment related factors

Total dose of cisplatin: Study by Vera-Llonch et al reported an increased frequency, severity, and duration of oral mucositis with concurrent chemoradiotherapy, with grade III-IV oral mucositis ranging from 30% to 84%. Incidence

of grade III and grade IV oral mucositis were reported in 80% and 39% respectively in patients of head and neck cancers respectively.[17] In our study, cumulative dose of cisplatin less than or equal to 200mg observed in 29 patients and 21 patients received more than 200mg of cisplatin as total dose. Twenty patients received less than or equal to 200mg of cisplatin had grade III & IV oral mucositis. Correlation between cumulative dose of cisplatin and oral mucositis was not statistically significant (p=0.39). In study by Hernández-Fernández A et al the frequency of mucositis and its severity are fundamentally dependent upon the type, duration and dose of chemotherapy used.[5]

Chemotherapy cycles: As reviewed by Elting et al mucositis can lead to a dose reduction of chemotherapy in 23%- 28% of cycles. These dose reductions are a major source of concern because they can directly diminish cure rates and patient survival.[10] In our study, 40 patients who received less than 5 cycles, among them 26 patients had grade III & IV oral mucositis, was not associated with poorer prognosis (p=0.76). A longer follow up may be needed to see the pattern of failure.

Radiotherapy dose: For head and neck cancers, a radiation dose of more than or equal to 66 Gy is considered radical/curative. Patients receiving less than the above desired dose are at a risk of having higher incidence of residual disease and are associated with poor prognosis. In our study, 16 out of 26 patients receiving > 66Gy had grade III & IV oral mucositis.

Overall treatment time: Patients who are unable to receive the prescribed treatment in its designated course of time have a higher risk of residual disease. The ideal overall treatment time in patients receiving conventional radiotherapy is 7 weeks (49 days). In Vera Llonch study, patients with oral mucositis had more unplanned breaks in radiation therapy and hospital admissions.[17] Studies by (Trotti et al and Russo et al) commented on oral mucositis is associated with a high rate of hospitalization and may interfere with the delivery of programmed treatment plans.[1,21] In this present study, 16 patients out of 23 patients whose overall treatment time > 49 days had grade III & IV oral mucositis and remaining 7 patients had grade I & II oral mucositis. No significant correlation between Overall treatment time and oral mucositis was found (p=0.66).

Treatment outcome

Oral mucositis and clinical response: Study by Vera Llonchet al high grade oral mucositis patients were associated with partial response in the treatment due to delay in treatment and many unplanned breaks.[17] The correlation between grade of oral mucositis and treatment response was not significant in the present study (p=0.19). Follow up period was only six month in this present study. Longer follow up is needed to see the local recurrence.

CONCLUSION

Oral mucositis is common in head and neck cancer patients undergoing chemoradiation. Increased severity can disrupt the planned protocol and subsequent treatment failure. Further oral mucositis may increase cost of treatment in terms of increased supportive medication & hospitalization. Unfortunately, preventing and treating oral mucositis is difficult at best.

It is critically important to develop and validate methods that can be used to quantify oral mucositis and develop targeted interventions to reduce this particular adverse effect of cancer treatment.

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