Oral Mucositis in Patients Undergoing Hematopoietic Stem Cell Transplantation

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ABSTRACT

Objective: To determine the factors affecting the frequency and severity of oral mucositis are following hematopoietic stem cell transplantation.

Study Design: Descriptive study.

Place and Duration of the Study: Armed Forces Bone Marrow Transplant Centre Rawalpindi, from September 2020 to February 2022.

Methodology: Patients who underwent allogenic stem cell transplantation were enrolled. Patients were analysed based on history and examination for oral mucositis (OM) as per the WHO mucositis scale, from the start of conditioning chemotherapy till discharge, total duration of mucositis and type of medication were noted. Its association with risk factors like age, gender, conditioning chemotherapy, methotrexate (MTX) for GVHD prophylaxis, and prior history of irradiation was determined.

Results: Mean age of the 72 transplant recipients was 21.9 ± 14 years, with 48 males and 24 females. The common underlying diseases were beta-thalassemia major (30.6%, n=22), acute lymphoblastic leukaemia (n=15, 20.8%), aplastic anaemia (n=10, 13.9%), and multiple myeloma (n=8, 11.1%). The frequency of mucositis in those aged under 15 years was 79.3% (n=23) and in those older than 15 years was 74.4% (n=32). Frequency of mucositis was statistically significant in patients who received myeloablative conditioning regimen (85% *vs.* 20%, p <0.01), and who had prophylactic. MTX (91% *vs.* 48%, p<0.01) and who had prior craniospinal (CSI) radiation (100% *vs.* 70.2%, p=0.01). There was no statistical significance between stem cell dose (CD34/TNC) and mucositis. Severity of mucositis was significantly greater in Allogenic *vs.* auto HSCT (p=0.04). All the patients with mucositis required analgesics for pain management.

Conclusion: Oral mucositis is a common but potentially debilitating complication of stem cell transplant, requiring opioid analgesia in a significant number of cases. Myeloablative conditioning, prophylactic MTX, and prior CSI are significantly associated with mucositis in transplant patients.

Key Words: *Hematopoietic stem cell transplantation (HSCT), Oral Mucositis, Myeloablative conditioning, Methotrexate, Analgesia*.

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INTRODUCTION

There are a number of benign and malignant haematological illnesses for which hematopoietic stem cell transplantation (HSCT) has the potential to be a therapeutic treatment. Oral mucositis (OM) is a serious complication affecting both allogenic and autologous transplant recipients causing significant morbidity.[1] Injuries to the submucosal endothelium cells, mucosal epithelial cells, and connective tissues all contribute to the development of oral mucositis in immune-compromised patients due to the toxic effects of conditioning chemotherapy, radiations and drugs (methotrexate).[2]

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The incidence of OM range from 75-100% following myeloablative conditioning (MAC) regimens.[3] Studies reveal that acclimatizing regimens having high doses of cyclophosphamide, melphalan, and busulfan with TBI (total body irradiation) are linked with intricate oral mucositis.[4] In contrast, the incidence reduces to 30-50% in patients treated with conditioning regimens without TBI.[5] Similarly, the severity and duration of OM are both reduced when reduced intensity conditioning (RIC) is applied.[6]

Damaged oral mucosa provides a site through which infectious agents and inflammatory mediators can enter the bloodstream, leading to increased risk of systemic infections.[7] Once ulcerations develop, systemic infections such as sepsis bacteremia, and fungemia pose a greater threat to patients with neutropenia.[8]

Despite considerable impact of OM, there is currently no foolproof method of protecting against OM by the use of preventative measures.[9] Some studies have shown the beneficial effects of keratinocyte growth factor and cryotherapy.[10] OM is debilitating and may require opioid analgesia for pain relief. Manage-

ment of oral mucositis is largely supportive, occasionally requiring parenteral nutrition.

There is limited number of transplant centres in Pakistan with scarce data on transplant complications. Currently, no published data is available regarding mucositis during the course of HSCT. The aim of this study was to assess the incidence and risk factors of mucositis in patients undergoing HSCT. This basic yet essential study would guide transplant physicians in tailoring conditioning regimens and taking preemptive/prophylactic measures to reduce the severity of mucositis.

METHODOLOGY

This is a descriptive study conducted at the Armed Forces Bone Marrow Transplant Centre, from 1st September 2020 to 28th February 2022. Patients aged 01-65 years of both genders undergoing bone marrow transplantation whether autologous or allogenic for the first time were included. Patients undergoing second or third HSCT and patients not consenting to be included in the study were excluded. Approval was taken from the Hospital's Ethical Review Committee for the commencement of this study on 16th August 2022 (IRB/FCPS-014/AFBMTC/Approval/2022). Severity of oral mucositis was defined as per WHO oral toxicity scale, separating mucositis into 5 grades as Grade 0 = No oral mucositis, Grade 1 = oral soreness and erythema, Grade 2 = oral ulcers patients able to take solids, Grade = 3 ulcers patients able to take liquids only, Grade 4 = oral alimentation not possible.[11]

Patients were analysed daily from the start of conditioning chemotherapy till discharge. Age, gender, Body mass index (BMI Kg/m^2), conditioning chemotherapy, use of methotrexate (MTX) for GVHD prophylaxis, and previous history of irradiation were considered as risk factors. Total duration of mucositis from the start of symptoms till resolution was also noted. Amount and type of analgesia required (paracetamol, tramadol, morphine bolus or infusion) was documented.

Statistical analysis was completed by using the Social Science Statistical Software (SPSS v26). Both qualitative and quantitative variables were subjected to descriptive statistics analysis. For quantitative variables, means and variances were determined. *i.e* BMI, age, and duration of disease. For qualitative variables, frequency and percentage were calculated *i.e.* age, gender, oral mucositis, grades of oral mucositis, MTX, MAC or RIC conditioning, irradiation, and analgesia used. Pearson chi-square test was used to determine the association of risk factors with mucositis. A p-value of less than 0.05 was taken as statistically significant.

RESULTS

The mean age of the 72 patients was 21.9 ± 14 years. Twenty nine patients (40.3%) were younger than 15 years while 43 patients (59.7%) were above 15 years of age. A total of 48 (66.7%) were males and 24 (33.3%) females. The most common underlying disease was beta-thalassemia major (BTM) (30.6%, n=22), acute lymphoblastic leukaemia (ALL, n=15, 20.8%), aplastic anaemia (AA, n=10, 13.9%), and multiple myeloma (MM, n=8, 11.1%). There were 6 (8.3%) cases of acute myeloid leukaemia (AML), 5 (6.9%) of chronic myeloid leukaemia (CML), 4 (5.6%) of Hodgkin lymphoma (HL), and 2 (2.8%) cases of non-Hodgkin lymphoma (NHL).

Table I: Patients characteristics, underlying diagnosis and transplant details.

Characteristic	Mean±SD
Age	21.9 ±14 years
Body Surface Area	1.40 ±0.5 m^2
Gender Distribution	Frequency
Male	66.7% (n=48)
Female	33.3% (n=24)
Age Group	Frequency
<15 Years	(n=29, 40.3%)
>15 Years	(n=43, 59.7%)
Underlying Diagnosis	Frequency
BTM	(n=22, 30.6%)
ALL	(n=15, 20.8%)
AA	(n=10, 13.9%)
MM	(n=8, 11.1%)
AML	(n=6, 8.3%)
CML	(n=5, 6.9%)
HL	(n=4, 5.6%)
NHL	(n=2, 2.8%)
Type of Transplant	Frequency
Allogenic	(n=58, 80.6%)
Autologous	(n=14, 19.4%)
Conditioning Regimen	Frequency
MAC	(n=62, 86%)
NMA or RIC	(n=10,14%)
Source of Stem Cells	Frequency
BMH	(n=46, 63.9%)
PBSC	(n=20, 27.8%)
BMH+PBSC	(n=06, 8.3%)
Stem Cell Dose	Mean±SD
TNC Dose	$5.47x10^8$/Kg±2.82
CD34Dose	$5.94x10^6$/Kg±4.32
Other Risk Factors	Frequency
Methotrexate	65.3 %(n=47)
Irradiation	20.8 %(n=15)

Most of the patients (80.6%, n=58) underwent allogenic stem cell transplant (full matched 54, haploidentical 4), while autologous transplant was done in 19.4% (n=14). MAC regimen was used in 86% (n=62) patients, while the rest (14%, n=10) had non-myeloablative (NMA) or RIC conditioning regimen. The source of stem cell was bone marrow harvest (BMH) in 63.9% (n=46), peripheral blood stem cells (PBSC) in 27.8% (n=20), and combination of BMH and PBSC in six (8.3%) patients. Mean total nucleated cells (TNC) dose was 5.47 x 10^8/Kg ± 2.82 and mean CD34 dose was 5.94 x 10^6/Kg ± 4.32. Fifteen (20.8%) patients had prophylactic craniospinal irradiation (CSI) with dose of 18-24Gy. MTX for GvHD prophylaxis was given to 65.3% (n=47) patients. Patient characteristics, underlying diagnosis, type of transplant, conditioning regimen, source of stem cells and other risk factors are given in Table I.

Mucositis was reported in 76.4% (n=55) patients, starting at median day 5 (range 1 -13) post-stem cell infusion. Severity of mucositis peaked at a median day 7 (4 -14). Four patients

(5.6%) had grade I, 18 (25%) grade II, 30 (41.7%) grade III, and 3 (4.2%) had grade IV mucositis as shown in Figure 1. Median duration of symptoms was 7 days (range 1 – 20). All the patients with mucositis required analgesics for pain management, which was morphine in 47.3% (n=26), Tramadol in 27.3% (n=15) and acetaminophen in the remaining 25.4%, (n=14).

Table II: Correlation of risk factors and mucositis.

Mucositis Variables	Yes	No	Chi Sq.
Conditioning type			
MA	85%	15%	P: <0.001
NMA	20%	80%	
Exposure to Radiation (Cranio-spinal)			
Yes	28.83%	0	P: <0.001
No	55.56%	23.61%	
MTx as GvHD prophylaxis			
Yes	58.33%	6.94%	P: <0.001
No	18.06%	16.67%	

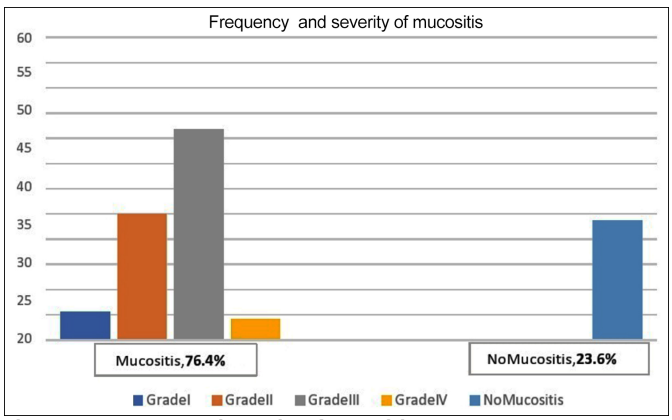

Figure 1: Frequency and severity of mucositis.

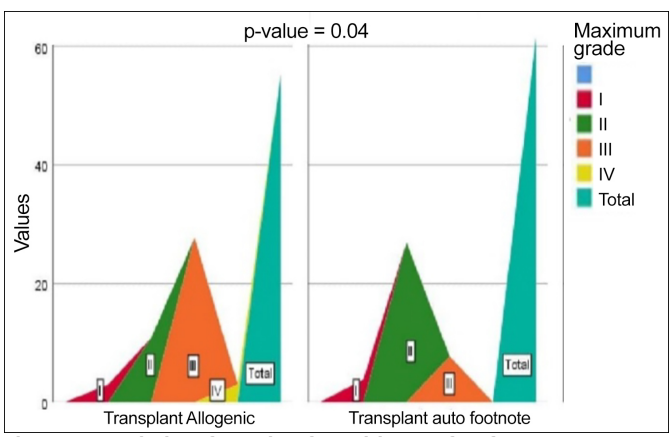

Figure 2: Correlation of severity of OM with type of graft.

When stratified for age, the incidence of mucositis in patients younger than 15 years was 79.3% (n=23) and 74. 4% (n=32) in those older than 15 years (p = 0.63). The frequency of OM in male and female patients was 72.9% (n=35) and 83.3% (n=20), respectively (p=0.32). It was 85% in patients who received MAC regimen and 20% in those who had NMA or RIC (p<0.01) as depicted in Table II. All patients (n=15) who received prior CSI developed mucositis *vs.* 70.2% (n=40) who had no CSI (p = 0.01) as shown in Table II. Frequency of oral mucositis in patients who received MTX was 91% (n=42) *vs.* 48% (n=13) who did not (p<0.01). Upon analysis of transplant type, the mucositis was more in allogenic *vs.* auto HSCT (80.3% *vs.* 62.5%, p=0.13). Severity of mucositis was more in allogenic *vs.* auto HSCT (p=0.04) as shown in Figure 2.

DISCUSSION

HSCT is increasingly used to treat both malignant and nonmalignant diseases and conditions, and has gained acceptance as a therapeutic approach. There are many complications of HSCT one of which is oral mucositis. It is attributed to the toxic effects of conditioning chemotherapy, radiations, and methotrexate used for GVHD prophylaxis. This study included 72 patients who underwent allogenic or autologous stem cell transplant for a variety of indications. The frequency of oral mucositis was 76.4% starting at median of day 5 post stem cell infusion and persisted for a median of 7 days. The findings compare favourably to those reported in international studies. An Iranian study reported incidence of oral mucositis in 60.7% patients who underwent HSCT. Symptoms started on days 5.2±2.4 with mean duration of symptoms for 9.9±3.9 days.[12] In a multicentre study from Italy, Vagliano *et al.* reported 71.4% mucositis.[13]

In this study, 30.6% patients had mild to moderate (Grade 1-2) mucositis while severe mucositis (Grade 3-4) was observed in 45.9% patients. A similar incidence (39.4%) of severe mucositis was reported by Vagliano *et al.* in adults undergoing allogenic transplant.[13] In the present study, stratification for age showed no significant difference between adult and paediatric patients, respective frequencies of 74.4% and 79.3% (p=0.63). However, Vagliano reported a higher incidence of mucositis in adult population (39.75 *vs.* 16.4%).[13] Similarly, the occurence of mucositis in male and female patients (72.9% and 83.3%, respectively) was not statistically significant. Valeh *et al.* found a significantly higher incidence of oral mucositis in female (71.2%) versus male (54%) patients (p=0.03).[12] However, there was no statistically significant difference in mucositis severity (p=0.07) or duration (p=0.38) between the genders.

Patients who were given a certain type of antibiotic had a higher risk of developing mucositis, according to the results of the current study MAC regimen (85% *vs.* 20%, p<0.01), who have received methotrexate as part of GvHD prophylaxis (91% *vs.* 48%, p<0.01), or who had prior CSI irradiation (100% *vs.* 70.2%, p=0.01). In a systematic review including 14 studies, Chaudhry *et al*. found that patients receiving MAC were 73% more likely to develop oral mucositis. They also noted a significantly greater frequency of mucositis among patients who received MTX (83.4%) compared to those who did not (55.4%, p=0.001).[14] Andrade *et al.* retrospectively analysed 32 patients who underwent HSCT with TBI-based myeloablative conditioning and reported 64% mucositis. He found incidence and severity of mucositis were lower in

patients who received methotrexate as part of the conditioning regimen compared to post-transplant cyclophosphamide.[15] The authors have documented higher incidence of mucositis in patients undergoing allogenic stem sem transplant than ASCT(p-value=0.04). The overall rate in the UK study was 2.88, which is also statistically significant (p=0.001).[15]

There is no published data from Pakistan related to complications of HSCT including mucositis, this one being the first one to the best of the authors' knowledge. It showed a significant morbidity burden that mucositis carries for stem cell transplant recipients. The results of this study will contribute to the better management of patients undergoing HSCT by devising pre-emptive strategies to lessen the effect of major contributing factors for mucositis such as MAC, MTX, and CSI.

CONCLUSION

Oral mucositis is a common but potentially debilitating complication of stem cell transplant, requiring opioid analgesia in a significant number of cases, irrespective of the patient's age or gender. Myeloablative conditioning, use of MTX for GVHD prophylaxis and prior CSI are the major risk factors for mucositis in transplant patients.

ETHICAL APPROVAL:

Approval was taken from Hospital Ethical Review Committee for the commencement of this study on 16th August 2022 (IRB/FCPS-014/AFBMTC/Approval/2022).

PATIENTS' CONSENT:

Informed consent were obtained from the patients to publish the data.

COMPETING INTEREST:

The authors have no competing interest to disclose.

AUTHORS' CONTRIBUTION:

MA: The acquisition, drafting the work and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
AA: Data collection, analysis, and interpretation of data for the work.
TK, MAK: Revising it critically for important intellectual content.
MH: Conception and design of the work.
YA: Final review.
All the authors have approved the final version of the manuscript to be published.

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