Evaluación longitudinal de la mucositis oral en el trasplante de células madre hematopoyéticas: un estudio piloto

Longitudinal evaluation of oral mucositis in hematopoietic stem cell transplantation: a pilot study

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RESUMEN

Objetivo: *describir la incidencia y el puntaje de la mucositis oral (MO) y las morbilidades relacionadas en individuos sometidos a trasplante de células madre hematopoyéticas (TCMH) a lo largo del período de inmunosupresión.* ***Métodos:*** *Los sujetos con enfermedades onco / hematológicas, mayores de 14 años, sometidos a TCMH alogénico fueron evaluados diariamente por la presencia y clasificación de OM, nivel de dolor, disfagia, disgeusia y xerostomía. El examen comenzó dos días antes de la infusión de células madre hematopoyéticas y finalizó veinte días después. La OM se clasificó de acuerdo con la escala de la OMS y se utilizó la escala analógica visual (EVA) para medir el nivel de dolor.* ***Resultados:*** *se reclutaron 23 individuos, el 83% con enfermedades malignas y el 91% con OM. La mediana del grado máximo de OM fue 3 y el nivel máximo de dolor fue 9. Hubo una mediana de 11 días de uso de medicación opioide. Los sujetos que tuvieron el mayor número de días con dolor en la boca alcanzaron el grado máximo de OM y el mayor número de días y el uso de opioides.* ***Conclusión:*** *Hubo una alta incidencia y puntuaciones más altas de OM, pérdida de masa corporal y dolor en esta muestra.*

PALABRAS CLAVE

Mucositis Oral; Trasplante de células madre; Neoplasmas hematológicos.

ABSTRACT

Aim: *To describe the oral mucositis (OM)` incidence and score, and related morbidities in individuals submitted to Hematopoietic Stem Cell Transplantation (HSCT) throughout the immunosuppression period of time* ***Methods:*** *Subjects with onco / hematological diseases, older than 14 years, submitted to allogeneic HSCT were daily evaluated by the presence and classification of OM, pain level, dysphagia, dysgeusia and xerostomia. The examination started two days before the infusion of hematopoietic stem cells and ended twenty days later. The OM was classified according to the WHO scale and visual analog scale (VAS) was used to measure pain level* ***Results:*** *Twenty-three individuals were recruted, 83% with malignant diseases and 91% had OM. The median of maximum OM degree was 3 and the maximum pain level was 9. There was a median of 11 days of opioid medication use. The subjects who had the highest mean number of days with mouth pain reached the maximum degree of OM and higher number of days and opiod use.* ***Conclusion:*** *There was a high incidence and high scores of OM, loss of body mass and pain in this sample.*

KEY WORDS

Oral mucositis; Stem Cell Transplantation; Haematological neoplasms.

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INTRODUCTION

The Hematopoietic Stem Cell Transplantation (HSCT) is a therapeutic procedure to treat onco / hematological diseases (Armitage, 1994; Lange *et al.*, 2006; Ribeiro *et al.*, 1996; Ruiz-Argüelles *et al.*, 2015). Prior the infusion of hematopoietic stem cells, an immunosuppressant regimen is necessary for death of bone marrow cells and preparation for reconstitution (Armitage, 1994; Bacigalupo *et al.*, 2009). The most often conditioning regimens used for HSCT are reduced-intensity conditioning (RIC) and myeloablative (MA), and both can induce OM (Bacigalupo et al., 2009; Bardellini *et al.*, 2013; Chaudhry *et al.*, 2016; Turner *et al.*, 2010). OM is an inflammation of gastrointestinal tract mucosa and its main cause is the chemotherapeutic conditioning prior to HSCT (Haverman *et al.*, 2014; Stephen T Sonis, 2012; Stephen T. Sonis, 2012). OM can leave malnutrition, bacteremia, psychological alterations, increase of hospitalization days and, often, failure to finish immunosuppressant regimen (Haverman *et al.*, 2014; Peterson *et al.*, 2011; Vera-Llonch *et al.*, 2007) . OM is commonly evaluated by World Health Organization (WHO) Scale, which considers objective and subjective variables (WHO, 2017).

Although there are several clinical studies about OM, few studies evaluate OM daily during the immunosuppressant period. In order to establish strategies to improve the patient's quality of life during the immunosuppressive phase it is required to evaluate the OM degree and its consequences throughout this period. Therefore, the aim of this study was to describe the incidence, severity of oral OM and related morbidities in individuals submitted to HSCT throughout the immunosuppression period.

Table 1: Patients characteristics about medications, disease and transplantation.

VARIABLE	n (%)
Sex	
Male	12 (52)
Female	11 (48)
Disease	
Malignant	19 (83)
Benign	4 (17)
Conditioning regimen	
Myeloablative	21 (91)
Reduced Intensity Conditioning	2 (9)
Medications before HSCT	
Chemotherapy	15 (65)
Immunosuppression	3 (13)
Tirosin Kinase Inhibitor	2 (9)
Azacitidin	1 (4)
No treatment	2 (9)
Transplantation type	
Relatated Donor	11 (48)
Non-Related Donor	10 (42)
Haploidentical	2 (10)
HSCT source	
Bone Marrow	19 (83)
Peripheral Blood	4 (17)
Immunoprophylaxis	
CSA + MTX	20 (87)
CSA + MMF + CFA	3 (13)
Presence of oral mucositis	
Yes	21 (91)
No	2 (9)

ECSA = Cyclosporin; MTX= Methotrexate; MMF= Mycophenolate; CFA= Cyclophosphamide.

METHODS

DESIGN

This is a longitudinal descriptive study conducted at the Bone Marrow Transplantation Unit of the Hospital de Clínicas of Federal University of Parana, Curitiba, Parana, Brazil, and was approved by the local Research Ethics Review Committee (number: 1.431.294).

Individuals' recruitment was performed when they were at the beginning of the conditioning regimen prior to HSCT.

SUBJECTS

Individuals with onco / hematological diseases, older than 14 years, both gender submitted to allogeneic HSCT were invited to participate of the study.

The participants agreed and signed the Free and Informed Consent Term / Informed Assent Term. Data were collected from March to October 2016.

PROCEDURE

A trained dentist evaluated all participants. The presence and grade

Table 2: Alterations between the grade of Oral Mucositis

	RAL MUCOSITIS GRADE			
	0	**II**	**III**	**IV**
Cases (n)	2	4	9	8
Sex (n)				
Male	2	0	7	3
Female	0	4	2	5
Previous chemotherapy (n)				
Yes	2	1	7	6
No	0	3	2	2
Conditioning regimen (n)				
TBI 1340+CFA	0	1	3	3
BUS 16+CFA	0	0	3	5
BUS12+CFA	1	1	2	0
RIC	1	0	1	0
Others	0	2	0	0
Oral Complains (%)				
Dysphagia	0	100	100	100
Dysgeusia	50	33.3	88.9	75
Xerostomia	50	33.3	66.7	75
Days with oral pain (mean±SD)	0	10±3.1	14±4	19±3.4
Days with OM (mean±SD)	0	12±12.6	15±5.1	19±3.5
Opiods (mean±SD)				
Maximum dose(mg/day/ IV)	3	25±10	40±12.6	71±6.1
Days of use	1	9±3.2	12±4.7	15±3.2
BMI (mean±SD) *				
Initial	21.8±1.4	30±6.3	23.6±6.9	28.1±8.9
Final	21.9±1.5	28.3±5.6	22.1±6.1	25.5±7.4
Difference (Final – Initial)	0.13±0.1	- 1.4±0.9	- 2.3±1.2	- 3±1.5
Hospitalization time (in days, mean±SD)	39±19.8	36±7.5	36±4.4	37±4.6

BMI= Body Mass Index; TBI 1320= Total Body Irradiation 1320 rads; CFA = Cyclophosphamide 120 mg/Kg; BUS 12/16= Busulfan 12/16 Mg/Kg; Fin.=final; In.=Initial * = p>0,05 ANOVA

of OM, pain level, dysphagia, dysgeusia and xerostomia were assessed daily. The examination started two days before the infusion of hematopoietic stem cells and ended twenty days later. At the first day, all patients received oral hygiene and OM care instructions. The OM was classified according to the WHO scale[13] and visual analog scale (VAS) was used to measure pain level. The participants answered questions about dysphagia, dysgeusia and xerostomia. Clinical records were used to collect demographical data and to verify hematological disease, medications, patient's diet and Body Mass Index (BMI).

DATA ANALYSIS

Data were tabulated and organized using Software Statistical Package for the Social Sciences (SPSS) 20.0. The Shapiro Wilk tests were used to verify the normality of the sample. Variance Analysis (ANOVA) and post hoc of Tukey were used to compare the BMI with maximum degree of OM. For statistic significant results was considered $p < 0.05$.

RESULTS

The initial sample was composed of 25 participants, of whom two were excluded. One had septic shock and the other one refused to participate. The median age was 31 years old (min. 14- max. 55) and male adults were predominant in the sample (52%). The majority of individuals had malignant diseases (83%) and MA conditioning (91%). Sixty five percent of the participants underwent chemotherapy prior the HSCT. Regarding the type of transplantation, 11 were related

donor (48%), the main source used was the bone marrow (83%) and the most common immunoprophylaxis regimen was Ciclosporin + Methotrexate (Table 1).

The incidence of OM was 91% (Table 1). The median number of days with OM among individuals was 14 days (min. 0 – max. 26 days), while the median number of days with oral pain was 13 days (min. 0 – max. 25 days). On the other hand, the median OM grade, according to the WHO scale, was 3 (min. 0 – max. 4) and the maximum pain level was 9 (min. 0 – max. 10). Opioid medication was used for 11 days (min. 0- max. 21) and maximum dose used was 42 mg / day / EV (min. 0- max. 80mg / day / EV). The result of these variables can be found on chart 1.

Based on the WHO scale, most of the participants had a maximum grade 3 (39%) of OM, individuals with this maximum degree of OM had mean of days of hospitalization similar to the mean of the other scores. Most individuals with grade 3 and 4 OM underwent chemotherapy prior to HSCT (Table 2). The individuals who had the highest number of days with oral pain were also those who reached the maximum score of OM (19 days), stayed more days with OM, used opioid medication for more days (mean of 15 days ± 3.2) with higher doses (mean maximum 71 mg / Day EV ± 6.1). (Table 2).

The conditioning that had the highest average number of individuals with grade 4 OM was Busulfan (BUS) 16 mg/kg + Cyclophosphamide (CFA) 120mg/kg. (Table 2).

All individuals who had OM also had BMI reduction during the follow-up period. The mean loss of body mass from the beginning of hospitalization to the end was higher in individuals who reached

Table 3: Mean days with mucositis, pain and opioid medication according to conditioning regimens.

Conditioning	TBI 1320 +CFA	BUS 16+CFA	BUS12+CFA	OTHERS
Days with OM (mean+SD)	2	4	9	8
Days with mouth pain (mean+SD)	2 0	0 4	7 2	3 5
Days of opioid use (mean+SD)	12±3.4	15±3.8	5±3.7	9±6.3

Chart 1 Median of days with oral pain, oral mucositis (degree) and opioid medication.

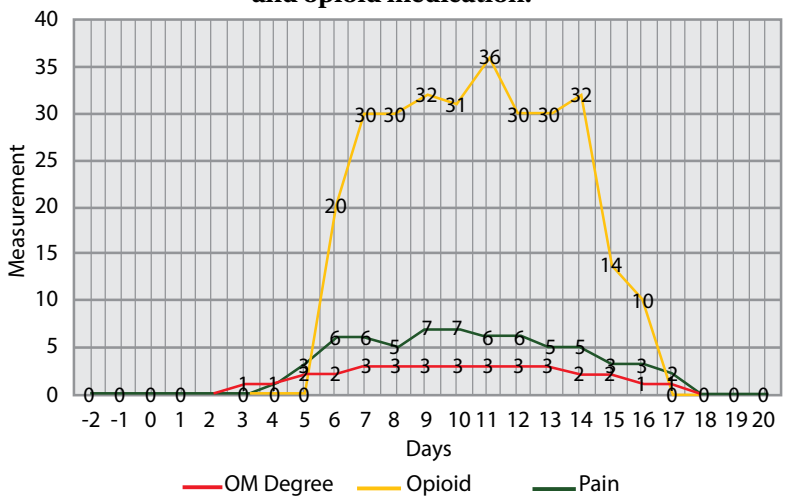


Chart 2 Mean of Body Mass Index difference on each oral mucositis grade

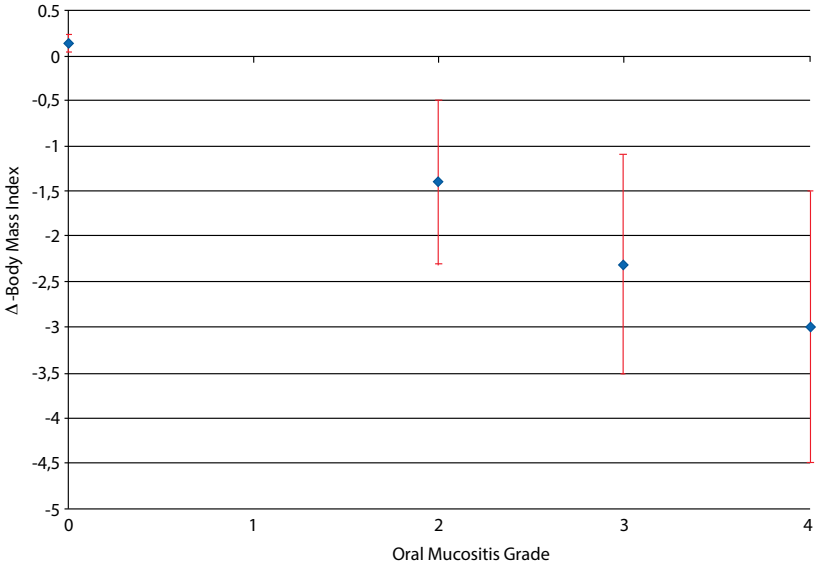
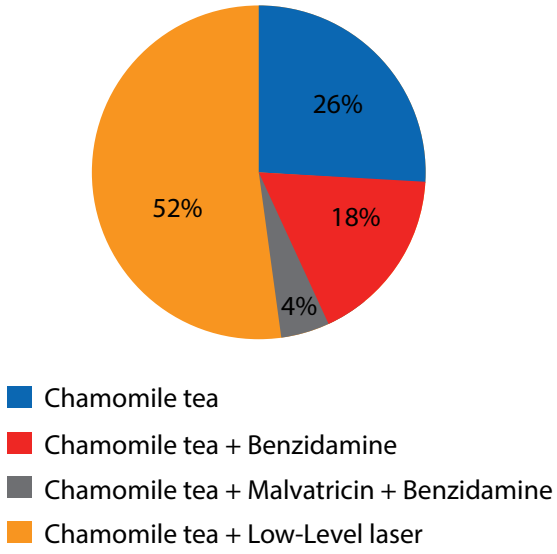


Chart 3 Distribution of the different treatments used by the patients for oral mucositis.



grade 4 OM. However, there was no statistical significance (p>0.05 ANOVA). On the other hand, the two patients without OM had an increase in BMI. (Chart 2)

The individuals who had the highest mean number of days with OM and oral pain were those who had total body irradiation (TBI) 1320 rads + cyclophosphamide (CFA) 120 mg / kg as conditioning (Table 3).

In addition to the opioid, which all patients with OM received, the most used treatment for OM was low-level laser associated with chamomile tea (52%) (Chart 3). Topical treatments for OM were individualized according to the preferences and possibility of each subject, regarding the severity of OM, individual values, socioeconomic condition and above all the patient's will.

DISCUSSION

The present study proposed to evaluate the incidence and degree of OM, and disorders related to it in individuals submitted to allogeneic HSCT. The most important findings were the high incidence OM and the correlation between the OM severity degree, according to WHO scale, with the use of opioid medication and BMI. Individuals with higher OM scale values needed more opioid medication and lost more weight.

OM is a frequent condition in individuals submitted to HSCT, which affects their quality of life (Silva *et al.*, 2015; Vera-Llonch et al., 2007). In the present sample there were a great number of participants with leukemia, consequently, the conditioning regimens were mostly MA, which could explain the high incidence of OM (Eslami *et al.*, 2016; Ramírez-amador et al., 2010; Small *et al.*, 2007; Wojciechowicz *et al.*, 2014).

The use of MTX as immunoprophylaxis may also have been a contributing factor to OM high incidence due to its high cytotoxic potential in cells with rapid multiplication. In addition, MTX is responsible for the delay of repair of the tissue damaged by chemotherapeutic conditioning (Ahmed *et al.*, 2017; Cutler *et al.*, 2005; Knoll *et al.*, 2016; Matsukawa *et al.*, 2016; Ramírez-amador *et al.*, 2010; Small *et al.*, 2007).

When compared to the total of days of hospitlization, a significant average of days with OM, oral pain and opioid medication were demonstrated. This average changes when participants are segregated according to the maximum OM grade: Grade 4 individuals were affected with longer periods with OM, had more oral pain, more opioid using and with higher dosage than patients with lower scores.

There was a greater BMI loss in patients who reached grade 3 and 4 OM, although no statistical significance was detected (Table2).

Regarding the conditioning regimen, individuals who used BUS 16 or TBI 1320 had a higher degree of OM (Table 1). Although most of the participants with grade 3 and 4 OM used BUS 16, who had a longer mean of days with OM and mouth pain were those that conditioned with TBI 1320, which suggests that such conditioning leads to prolonged toxicity. On the other hand, Chaudhry *et al.*(2016) performed a systematic review that evaluated the incidence and severity of OM in HSCT and found that there was a significant incidence of severe OM in both MA and RIC and those individuals who received TBI had more severe OM when compared to BUS. Nevertheless, it is important that individuals undergoing these types of conditioning receive extra oral.

Concerning the functional alterations in the mouth, there was a high incidence of dysgeusia and xerostomia in patients with grade 3 and 4 OM (Table 2). Boer (Boer *et al.*, 2009) already evaluated the

taste alteration of patients submitted to HSCT and verified that the situation continues as a late complication. Furthermore, Laaksonen et al.(Laaksonen *et al.*, 2011) studied longitudinally the saliva of patients for 24 months after HSCT, and also demonstrated some functional alteration in the mouth, concluding that hyposalivation is frequent and occurs more in MA conditioning and is reversible.

It is important to note that the use of opioid medication may often be associated with other painful episodes, not necessarily OM, so, it is important to evaluate other parameters, such as evaluation of mouth pain by VAS and the score of OM by the scale of WHO. Moreover, BMI should be used judiciously, especially in individuals with lean mass and / or water retention. In future studies it is suggested that body composition should be considered similarly to the study by Thomaz (ABESO, 2016; Thomaz *et al.*, 2015).

One limitation of this study is the small number of participants. Further studies with higher sample size are suggested to evaluate the risk factors for OM and thus to delineate a line of care for this condition.

Although OM is a self-limiting condition and resolves with decreasing of chemotherapy toxicity and consequent bone marrow regeneration, it is still a debilitating condition. Therefore, it is important to delimit its incidence, severity, risk factors and evolution time, for oral care can be implemented in the population at risk, in order to decrease the use of opioid medication and its side effects, improving the quality of life of this group.

CONCLUSION

A high incidence of severe oral OM was observed in this population during this period of time. Individuals with a maximum grade of OM 3 and 4 and greater dosages and longer time of opioid analgesia use.

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