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Impact of Oral and Gastrointestinal Mucositis on Body Weight Alterations during Hematopoietic Stem Cell Transplantation

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ABSTRACT

The aim of this study was to evaluate whether digestive tract mucositis is a predictive factor for body weight (BW) alterations during hematopoietic stem cell transplantation (HSCT). Data about characteristics of transplantation, initial nutritional conditions and gastrointestinal mucositis were collected from adult patients ($n = 105$) who underwent autologous and allogeneic HSCT. Oral mucositis (OM) was not a predictive factor for BW loss, but it was an independent factor for BW gain in autologous HSCT ($\beta = 0.329$, $P = 0.021$). Busulfan-fludarabine conditioning regimen ($\beta = 1.531$, $P = 0.011$) and gender ($\beta = 1.109$, $P = 0.038$) were significant independent risk factors for BW loss in allogeneic HSCT. Overall survival (OS) was significantly affected by the duration of OM in autologous HSCT (HR = 1.243, $P = 0.008$). In allogeneic HSCT, BW loss (HR = 1.308, $P = 0.049$) and diarrhea (HR = 1.139, $P = 0.012$) interfered significantly with OS. In conclusion, OM was not a risk factor for BW loss, but it influenced BW gain and had a negative impact on OS in autologous HSCT patients. Intestinal mucositis explained partially the BW loss and had a negative impact on OS in allogeneic HSCT.

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Introduction

Nutritional deficiencies are frequently expected during hematopoietic stem cell transplantation (HSCT), mainly due to an increased catabolic effect derived from the chemo-radiotherapy conditioning (1), which affects the protein and micronutrient metabolism (2). Energy expenditure is high during HSCT, reaching 130–150% of the energy expenditure recorded at baseline (2,3).

Mucositis in the gastrointestinal tract is one of the most common complications affecting directly the nutritional status during HSCT (1). This is an inflammatory condition resulting from the cytotoxicity effect caused by the HSCT conditioning regimen and graft-versus-host diseases (GVHD) prophylaxis, leading to destruction of the mucosal barrier localized in oral cavity, pharynx, esophagus, and gastrointestinal tract. High severity of mucositis can predispose to impairment of oral intake due to difficulties in mastication and swallowing. In addition, HSCT patients frequently have diarrhea as a result of damage to the intestinal mucosa, which shows reduction in the absorption capacity (4).

Weekly measurements of body weight and of percentage of body weight loss are recommended for assessment of nutritional status during HSCT (1). Although the ideal nutritional parameters for evaluation of the nutrition conditions in HSCT patients are not well-established (5), measurements of body weight can indicate the levels of catabolic condition and thus contribute to the adoption of methods for nutrition improvement (3).

The presence of severe oral mucositis (OM) leading to reduction of oral intake is key for decision-making when adopting nutritional support, including artificial nutrition (1,3). Due to its high morbidity, prevention and treatment of OM have been adopted in several transplantation centers worldwide, thus avoiding the presence of lesions with high grade of severity in various HSCT situations (6–8). In our center, an oral care protocol is rigorously applied in order to avoid infectious foci in the oral cavity, as well as to prevent and treat OM, improving the HSCT patient's quality of life (9). Based on our good clinical outcomes for OM patients (10), we hypothesized that the interference of OM with body weight alterations during HSCT would be absent or irrelevant. Other variables related to gastrointestinal mucositis rather than OM could be predictive factors for body weight alterations.

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Therefore, the aim of this study was to verify whether OM is a risk factor for body weight variations, especially body weight loss, during autologous and allogeneic HSCT. In addition, considering that malnutrition can be an independent risk factor for mortality after HSCT (1), we have also decided to verify whether body weight alterations and variables related to gastrointestinal mucositis had an impact on overall survival after HSCT.

Patients and Methods

This study was approved by the local Human Research Ethics Committee (protocol number 1904–13), being in accordance with international statutes on ethics in research involving humans as well as with the Helsinki Declaration.

Patient Selection

This a retrospective study of consecutive adult HSCT patients who attended the Hospital Israelita Albert Einstein (HIAE), Brazil. We selected medical records from patients who underwent autologous and allogeneic HSCT between 2012 and 2014. Exclusion criteria were the following: patients younger than 18 years old; medical records poorly describing all the variables related to gastrointestinal mucositis; absence of daily information about body weight and food intake; patients who refused to adopt the prescribed oral protocol, including application of low-level laser therapy and cryo-therapy when necessary; and patients who died during the HSCT.

Infection Prevention

All the patients received a protocol for infection prevention which included intravenous administration of acyclovir, fluconazole, levofloxacin, and sulfamethoxazole.

Oral care Protocol

An oral care protocol was daily applied for all patients in the pre- and peritransplantation periods. Before the conditioning regimen, the oral cavity was examined by a dental professional, who removed all the infection foci and sites with risk of mucosal injury. During transplantation, a dental professional monitored rigorously the oral hygiene of the patients and prescribed alcohol-free antimicrobial mouthwashes with enzymatic action, manual tooth-brushing, cocoa butter lip balm (three times a day), vitamin E (twice a day) in the case of dry lips, and dry mouth moisturizing in the case of xerostomia. Low-level laser therapy (once a day) was indicated for all the patients from the first day of conditioning regimen to the day of marrow engraftment (10). In the case of melphalan conditioning, cryo-therapy during melphalan infusion was also adopted for reducing the risk of OM (11).

Assessment of Mucositis in the Gastrointestinal tract

The severity of OM was examined daily by a dental professional using the following World Health Organization criteria: Grade 0 = none; Grade I = soreness and erythema; Grade II = erythema and ulcers without difficulty to swallow solid food; Grade III = ulceration, requiring only a liquid diet; and Grade IV = introduction of TPN. Number of days of OM was also recorded.

In addition to OM, the dental professional recorded all the symptoms present in the oral cavity, mainly any type of discomfort, xerostomia, increased sensibility of the oral mucosa, and taste alterations. Mucositis in pharynx and esophagus was recorded based on the patient's report about pain and discomfort in swallowing. The dental professional collected this information in detail in order to distinguish the presence of OM from mucositis in pharynx and esophagus. The frequency and length of diarrhea were also recorded, with negative antimicrobial culture and nauseas/vomiting being used for analysis of gastrointestinal mucositis.

Data Collection

The following data on HSCT patients were collected from their medical records: gender, age, type of HSCT, primary disease, conditioning regimen, GVHD prophylaxis, number of days of neutropenia, and duration of transplantation. Information about nutritional conditions at baseline was: body weight, body mass index (BMI), estimation of energy expenditure and protein intake, total serum proteins, and serum albumin levels. Daily value of body weight was collected from the first day of conditioning to the moment of discharge from the transplantation center. Minor and major values were used to calculate body weight loss and body weight gain in relation to the baseline. Data on gastrointestinal mucositis and related variables were the following: grade of OM, frequency/number of days of OM, pain/discomfort in oral cavity, pain/discomfort in pharynx/esophagus, xerostomia, nausea/vomiting, mucositis-related diarrhea, fever, opioid prescription, and total parenteral nutrition (TPN).

Statistical Analyses

Descriptive statistics was performed by using absolute and relative frequency for categorical variables, whereas mean, median, standard-deviation and range were used

for continuous variables. Autologous and allogeneic HSCT were analyzed in conjunction and individually, being compared by using χ^2 test, Fisher's exact test, and Student's *t*-test. Body weight loss and body weight gain were considered dependent variables. To analyze the predictive factors for body weight loss and gain, firstly we performed univariate analysis by using the Student's *t*-test. The independent variables with $P < 0.100$ were included in a multivariate regression linear model by using a stepwise procedure. We also analyzed the impact of body weight loss/gain and of other variables on overall survival (OS). OS was the time interval between the first day of HSCT and the moment of death, independently of the cause. Kaplan–Meier test was used for OS estimation, and log-rank test was applied for comparing different OS curves. Cox-proportional hazards regression was adopted for determination of factors interfering with OS. The significance level was set to 5%. We used R statistical software package (12) for all analyses.

Results

Patients and Transplantation Characteristics

From 2012 and 2014, 205 patients were attended at the Bone Marrow Transplantation Center of the HIAE. Based on the inclusion and exclusion criteria, we selected 105 patients in which 54 were of autologous and 51 of allogeneic HSCT (20 matched related-donor, 23 matched unrelated-donor, and 8 haploidentical transplantations). We excluded 100 patients because 63 were under 18 years of age and 37 did not have complete information about initial nutrition status and body weight variations. All the reviewed patients followed adequately the oral care protocol. Table 1 shows characteristics of the patients and HSCT. At the moment of the transplantation admission, the patients who underwent allogeneic HSCT had body weight ($P = 0.005$), BMI ($P < 0.001$) and protein intake requirement ($P = 0.014$) lower than those observed for patients who underwent autologous HSCT. Considering the whole sample, there was a relatively high frequency of overweight and obese patients (42.8% and 19.0%, respectively), but a low frequency of underweight patients (7.7%). In the autologous and allogeneic groups, the mean values at admission for serum total protein and serum albumin levels were slightly below from the normal values. In the allogeneic group, the numbers of days of transplantation and neutropenia were higher than those observed in the autologous group ($P < 0.001$ for both variables).

Table 2 shows body weight variations during the transplantation and the frequency of TPN prescription. In the allogeneic group, the median of body weight loss

Table 1. Clinical characteristics of the patients and hematopoietic stem cell transplantation.

	Autologous ($n = 54$)	Allogeneic ($n = 51$)	*P* value
Age (years) – mean ± SD	53.1 ± 14.5	49. 6± 16.1	0.234
Gender – *n* (%)			
Male	30 (55.6)	26 (51.0)	0.781
Female	24 (44.4)	25 (49.0)	
Baseline body mass (kg) – mean ± SD	82.7 ± 20.5	72.2 ± 16.0	0.005
Baseline body mass index (kg/m^2) – mean ± SD	27.6 ± 4.4	25.3 ± 4.8	<0.001
Baseline weight classification – *n* (%)			
Underweight (<18.5 kg/m^2)	1 (1.8)	3 (5.9)	0.198
Normal weight (18.5 to 24.9 kg/m^2)	14 (25.9)	22 (43.1)	
Overweight (25.0 to 29.9 kg/m^2)	25 (46.2)	20 (39.2)	
Obese (≥30.0 kg/m^2)	14 (25.9)	6 (11.8)	
Baseline energy intake (kcal) – mean ± SD	2226.0 ± 332.7	2007.3 ± 284.4	0.322
Baseline protein intake (g) – mean± SD	95.3 ± 32.6	78.1 ± 31.4	0.014
Baseline serum total proteins (g/dl) – mean ± SD	5.5 ± 0.9	5.7 ± 0.8	0.790
Baseline serum albumin (g/dl) – mean ± SD	3.12 ± 0.6	3.29 ± 0.4	0.123
Primary disease – *n* (%)			
Acute lymphoid leukemia	0 (0.0)	8 (15.7)*	<0.001
Acute myeloid leukemia	1 (1.9)	15 (29.4)*	
Chronic myeloid leukemia	1 (1.9)	2 (3.9)	
Aplastic anemia	0 (0.0)	4(7.8)	
Hodgkin lymphoma	6 (11.1)	4(7.8)	
Non-Hodgkin lymphoma	12(22.2)	5 (9.8)	
Multiple myeloma	27 (50.0)	2 (3.9)*	
Myelodysplastic syndrome	0 (0.0)	5 (9.8)*	
Myelofibrosis	0 (0.0)	4 (7.8)*	
Multiple sclerosis	4 (7.4)	0 (0.0)	
Others	3 (5.6)	2 (3.9)	
Chemotherapy regimen – *n* (%)			
BEAM	16 (29.6)	0 (0.0)*	<0.001
Busulfan and melphalan	5 (9.3)	0 (0.0)	
Busulfan and fludarabine	0 (0.0)	26 (50.0)*	
Busulfan and cyclophosphamide	0 (0.0)	2 (3.8)	
Cyclophosphamide and fludarabine	0 (0.0)	2 (3.8)	
Cyclophosphamide, fludarabine and TBI	0 (0.0)	7 (13.5)*	
Cyclophosphamide and ATG	7 (13.0)	0 (0.0)*	
Melphalan	26 (48.1)	0 (0.0)*	
Melphalan and fludarabine	0 (0.0)	4 (7.7)	
Fludarabine and TBI	0 (0.0)	4 (7.7)	
GVHD prophylaxis – *n* (%)			
Methotrexate, tacrolimus and ATG	–	5 (9.6)	–
Methotrexate and tacrolimus	–	24 (46.2)	–
Methotrexate and cyclosporin A	–	5 (9.6)	–
Cyclosporin A, MMF and tacrolimus	–	6 (11.5)	–
Cyclosporin A and MMF	–	9 (17.3)	–
MMF and tacrolimus	–	3 (5.8)	–
Days of transplantation – mean ± SD	21.5 ± 4.3	32.5 ± 6.9	<0.001
Days of neutropenia** – mean ± SD	8.4 ± 2.1	15.7 ± 6.9	<0.001

P-value for Student's *t* and χ^2-test. Significant when $P < 0.05$.
*Statistically significant when compared with Autologous group. SD, standard deviation; TBI, total body irradiation; BEAM, carmustine, etoposide, cytarabine, melphalan; ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil. **Absolute neutrophil count ≤500 cells/mm^3.

Table 2. Body weight variations and frequency of parenteral nutrition during hematopoietic stem cell transplantation.

	Autologous ($n = 54$)	Allogeneic ($n = 51$)	P value
Decrease on body weight			
Body weight loss (kg) – median (range)	1.8 (0.0–7.3)	2.7 (0.0–11.3)	0.014
Frequency of patients with body weight loss – n (%)	43 (79.6)	47 (92.2)	0.715
Frequency of patients with ≥5% body weight loss – n (%)	9 (16.6)	18 (35.2)	0.130
Increase on body weight			
Proportion (kg) – median (range)	2.4 (0.0–11.0)	1.7 (0.0–8.2)	0.126
Frequency of patients with body weight gain – n (%)	45 (88.9)	44 (86.2)	0.981
Frequency of patients with ≥5% body weight gain – n (%)	13 (24.0%)	8 (15.6)	0.523
Total parenteral nutrition prescription			
Frequency of patients – n (%)	6 (11.1)	16 (31.3)	0.039
Number of days – median (range)	5 (3–10)	11 (3–28)	0.005
Motifs to parenteral nutrition prescription – n (%)			
Pain in pharynx/esophagus	4 (66.7)	10 (62.5)	0.186
Pain in oral cavity	1 (16.7)	7 (43.7)	0.061
Nauseas/vomiting	0 (0.0)	2 (12.5)	0.243
Diarrhea	3 (50.0)	3 (x18.7)	1.000

P-value for Student's t, χ^2, and Fisher's exact tests. Significant when $P < 0.05$.

Table 3. Frequency of conditioning-related toxicity, fever, and opioid prescription during hematopoietic stem cell transplantation.

	Autologous ($n = 54$)	Allogeneic ($n = 51$)	P value
Oral mucositis			
WHO grade 0 – n (%)	23 (42.6)	7* (13.7)	0.002
WHO grades I and II – n (%)	28 (51.8)	34 (66.7)	
WHO grades III and IV – n (%)	3 (5.6)	10 (19.6)	
Number of days – median (range)	4 (1–14)	8 (2–19)	0.001
Dysphagia – pain/discomfort in oral cavity			
Frequency – n (%)	14 (25.9)	36 (70.5)	0.015
Number of days – median (range)	2 (1–17)	6 (1–16)	0.007
Dysphagia – pain/discomfort in pharynx			
Frequency – n (%)	27 (50.0)	39 (76.4)	0.209
Number of days – median (range)	0.5 (1–10)	6 (1–21)	0.016
Xerostomia			
Frequency – n (%)	23 (42.6)	23 (45.0)	0.987
Number of days – median (range)	4 (1–11)	7.5 (2–22)	0.038
Nauseas/vomiting			
Frequency – n (%)	33 (61.1)	34 (66.7)	0.688
Number of days – median (range)	4 (1–9)	5 (1–15)	0.032
Mucositis-related diarrhea			
Frequency – n (%)	46 (85.1)	37 (72.5)	0.690
Number of days – median (range)	6.5 (1–13)	6 (1–17)	0.974
Fever (>37.9°C)			
Frequency – n (%)	34 (62.7)	27 (52.3)	0.707
Number of days – median (range)	3 (1–15)	4 (1–17)	0.299
Opiod prescription			
Frequency – n (%)	18 (33.3)	24 (47.0)	0.449
Number of days – mean±SD	5 (1–12)	5.5 (1–21)	0.647

P-value for χ^2 test and Mann–Whitney test. Significant when $P < 0.05$.
*Statistically significant when compared with Autologous group.

was higher than that of the autologous group ($P = 0.014$). Body weight gain was similar between the two groups. The frequency of TPN prescription ($P = 0.039$) and the median number of days of TPN ($P = 0.005$) were higher in the allogeneic than in the autologous group .For both groups, the main cause for TPN prescription was pain in pharynx/esophagus, followed by pain in the oral cavity. In some patients, TPN was indicated due to other symptoms in the digestive tract, such as nauseas/vomiting and diarrhea, leading to nutritional disturbances that obligated the indication of TPN, although the oral intake was not totally compromised.

The median body weight loss in autologous patients who needed or not TPN was 1.7 kg (1.0–3.1 kg range) and 1.85 kg (0.0–7.3 kg range), respectively, without significant difference ($P = 0.763$). The median body weight gain in autologous patients who needed TPN was higher than that in patients without TPN (3.44 kg [0.8–11.0 kg] compared to 2.2 kg [0.0–9.9 kg]), but this difference was not significant ($P = 0.246$). For allogeneic patients, the median body weight loss in patients who needed or not TPN was 2.70 kg (0.0–8.4 kg range) and 2.75 kg (0.0–11.3 kg range), respectively ($P = 0.843$). The median body weight gain in the patients who needed TPN was higher than that in patients who did not need TPN (1.9 kg [0.1–4.8 kg] compared with 1.3 [0.0–8.2 kg]), but this difference also was not statistically significant ($P = 0.201$).

The frequencies of chemo-radiotherapy toxicity, fever, and opioid prescription are listed in Table 3. In the allogeneic group, the number of days of OM was higher than in the autologous group ($P = 0.001$), as well as the number of days of pain/discomfort in the oral cavity ($P = 0.007$), pain/discomfort in the pharynx ($P = 0.016$) and xerostomia ($P = 0.038$). In addition, the autologous group had the highest frequency of absence of OM (42.6% compared to 13.7%, $P = 0.002$). There were no significant differences between the groups with regard to frequency and length of mucositis-related diarrhea, fever, and opioid prescription.

Univariate and Multivariate Analyses

We have analyzed the association between body weight variation and independent variables related to the toxicity resulting from the chemo-radiotherapy conditioning. Table 4 shows the results of univariate analysis for body weight loss and gain in the autologous and allogeneic groups, whereas Table 5 lists the results of multivariate analysis for each group.

Table 4. Univariate analysis of body weight loss and gain during autologous and allogeneic hematopoietic stem cell transplantations.

	Autologous		Allogeneic	
	95% CI	*P* value	95% CI	*P* value
Body weight loss				
Gender	[−0.793]–[2.029]	0.247	[0.264]–[2.865]	0.019
Busulphan/fludarabine conditioning	–	–	[0.466]–[3.054]	0.008
Cyclosporin A, MMF and tacrolimus conditioning	–	–	[−3.482]–[−1.106]	<0.001
Number of days of pain in pharynx	[−1.807]–[1.344]	0.696	[−4.260]–[−1.010]	0.002
Number of days of oral mucositis	[−2.326]–[0.687]	0.151	[−5.054]–[−2.290]	<0.001
Number of days of diarrhea	[−4.598]–[−2.374]	<**0.001**	[−3.192]–[−0.430]	0.011
Number of days of neutropenia	[−6.970]–[−5.090]	<**0.001**	[−14.372]–[−10.702]	<0.001
Body weight gain				
Number of days of pain in pharynx	[−1.040]–[1.717]	0.514	[−5.692]–[−1.598]	<0.001
Number of days of pain oral cavity	[0.243]–[2.048]	**0.013**	[−4.123]–[−0.456]	0.001
Number of days of oral mucositis	[−1.652]–[1.175]	0.653	[−6.865]–[−2.830]	<0.001
Number of days of nauseas/vomiting	[−0.790]–[1.967]	0.259	[−2.664]–[−0.322]	0.013
Number of days of diarrhea	[−4.548]–[−1.313]	<**0.001**	[−5.023]–[−1.354]	<0.001
Number of days of neutropenia	[−6.759]–[−4.555]	<**0.001**	[−16.042]–[−11.292]	<0.001

CI, confidence interval; MMF, mycophenolate mofetil. *P*-values for Student's *t*-test. Significant when $P < 0.05$.

For the autologous HSCT, in a model of multivariate analysis by using stepwise linear regression, none of the significant variables listed in Table 4 showed significant association in an adjusted model. Therefore, we found no predictive variable for decreased body weight in patients who underwent autologous HSCT. With regard to body weight gain (Table 4), only the number of days of pain/discomfort in the oral cavity was found to be a significant independent risk factor for increased body weight in the autologous HSCT ($R^2 = 11.7\%$, $\beta = 0.329$, $P = 0.021$) (Table 5). In order to verify the influence of other variables related to body weight increase, we collected information about plasmatic levels of sodium as well as presence of renal and hepatic dysfunction. We found that 85.3% of the patients of autologous group with body weight gain exhibited hyponatremia during the transplantation ($P = 0.033$), only one patient (3.0%) in this condition had renal insufficiency, and none was diagnosed with hepatic veno-occlusive disease or other vascular alteration.

In a multivariate analysis for the allogeneic group (Table 5) by using a stepwise model and including all the significant variables (Table 4), only gender ($\beta = 1.109$, $P = 0.038$) and busulfan-fludarabine conditioning ($\beta = 1.531$, $P = 0.011$) were considered to be significant predictive factors for body weight loss. These independent factors can partially explain this condition in the allogeneic group ($R^2 = 33.3\%$, com $P < 0.001$). In relation to gender, the median weight loss for men was 3.5 kg (0.3–11.3 kg range) and for women 2.1 kg (0–6.4 kg range) ($P = 0.019$). None of the significant variables (Table 4) was capable to explain the body weight gain in the allogeneic group.

Overall Survival

Figure 1(a) shows the Kaplan–Meier OS curve for autologous and allogeneic groups. The 3-year OS rates for autologous and allogeneic HSCT patients were, respectively, 82.8% (95% CI = 68.0–91.1%) and 57.0% (95% CI = 40.8–70.4%) ($\chi^2 = 9.0$, $P = 0.002$). For analysis of predictive factors for OS, we performed a multivariate analysis by using the Cox proportional hazard model with the following variables: body weight loss and gain, gender, melphalan conditioning (only for autologous

Table 5. Risk factors of body weight loss and gain detected by multiple linear regression in autologous and allogeneic hematopoietic stem cell transplantations.

Variables	Coefficient (β)	SE	95% CI	*t*-Value	*P* value
Autologous – increase on body weight					
Intercept	2.448	0.484	[1.466]–[3.431]	5.060	<0.001
Number of days of pain/discomfort in oral cavity	0.329	0.136	[0.051]–[0.606]	2.409	0.021
			Adj $R^2 = 0.117$; $F = 5.804$; $P = 0.021$		
Allogeneic – decrease on body weight					
Intercept	2.084	0.599	[0.874]–[3.294]	3.476	0.001
Gender	1.109	0.518	[0.064]– [1.109]	2.141	0.038
Busulphan/fludarabine conditioning	1.531	0.576	[0.874]– [2.694]	2.655	0.011
			Adj $R^2 = 0.333$; $F = 8.684$; $P < 0.001$		

SE, standard error; CI, confidence interval; MMF, mycophenolate mofetil.

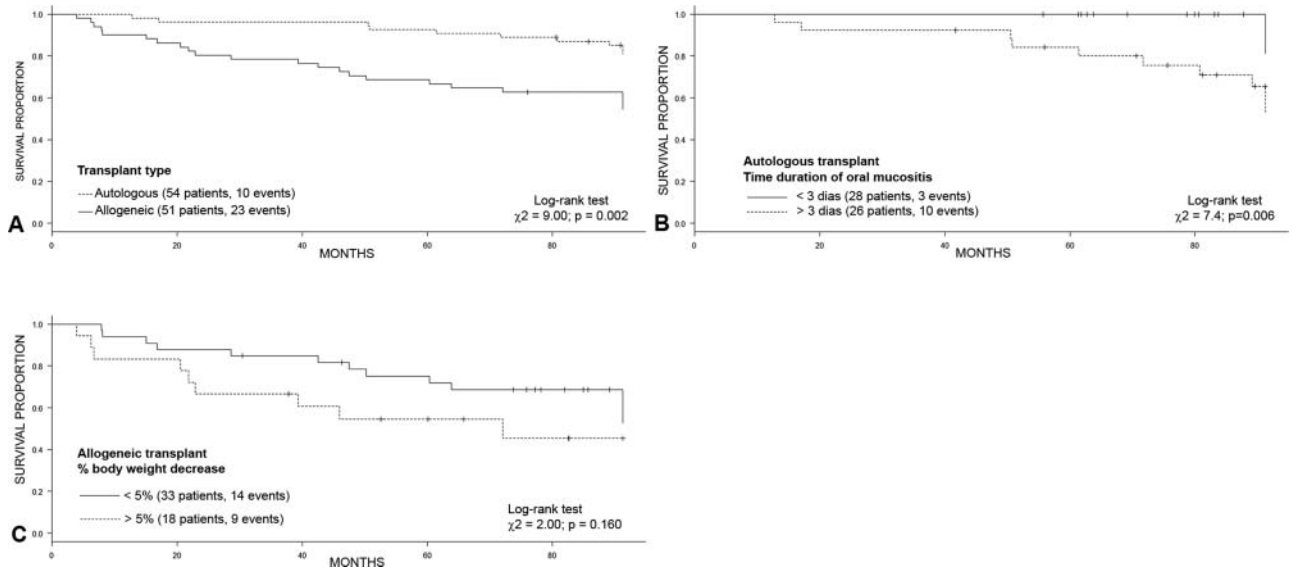

Figure 1. Kaplan–Meier curves for overall survival in relation to (a) autologous and allogeneic HSCT patients, (b) duration of oral mucositis in autologous HSCT patients, and (c) percentage of body weight loss in allogeneic HSCT patients.

HSCT), busulfan-fludarabine conditioning (only for allogeneic HSCT), GVHD prophylaxis with methotrexate/tacrolimus and cyclosporine/MMF/tacrolimus (only for allogeneic HSCT), and length of diarrhea, OM and pain/discomfort in the oral cavity and pharynx. These variables were chosen based on previous univariate analyses.

In the autologous group, the adjusted model showed that body weight loss and gain had no influence on OS, with number of days of OM being the only significant independent risk factor for OS (HR = 1.243, 95% CI (HR) = [1.056]–[1.464], $P = 0.008$). By comparing the Kaplan-Meier curves for median number of days of OM in the autologous group (< or >3 days), there was a significant difference between the curves ($\chi^2 = 7.4$, $P = 0.006$) (Figure 1b).

In the allogeneic group, body weight loss was a significant risk factor for OS (HR = 1.308, 95% CI (HR) = [1.147]–[2.404], $P = 0.049$). In order to evaluate the influence of a critical body weight loss on OS, we divided the patients into percentage decreases of body weight (i.e., <5% and ≥5%) during transplantation. The comparison of Kaplan-Meier curves (Figure 1c) did not reveal significant differences ($\chi^2 = 2.0$, $P = 0.160$), whereas the number of days of diarrhea was a significant risk factor for OS in the allogeneic group (HR = 1.139, 95% CI (HR) = [1.012]–[1.281], $P = 0.012$).

Discussion

The main objective of this study was to verify the impact of the gastrointestinal mucositis on body weight during HSCT and on OS. Some variables related to mucositis in the gastrointestinal tract (i.e., numbers of days of pain/discomfort in the oral cavity/pharynx and of OM) had no significant impact on body weight loss in both autologous and allogeneic HSCT patients.

It is possible that the impact of OM on body weight loss in this study has not been evidenced because in this study the majority of the patients had low grades or absence of OM, probably due to our oral care protocol (10,11). The patients with grades 0 to II did not show impairment in oral intake, although in some patients the OM grade II was manifested by ulcers in the oral mucosa. Probably the laser therapy, associated to daily careful oral hygiene, may have promoted analgesia and tissue repair, favoring a sufficient oral intake during the transplantation (10). In addition, the patients selected for our study showed a mild body weight loss, with median <5% of the body weight at baseline. Nutritional assessment and support are performed daily in our center, which also minimizes the body weight loss (1,3).Our results were in accordance with a prospective study with autologous and allogeneic HSCT patients, in which there was no correlation between body mass index reduction and incidence and severity of OM. Moreover, the mean body weight loss was about 2.5% in relation to the baseline (13).

Although there was a low mean weight loss and low grades of OM in both autologous and allogeneic groups, 31.3% of the patients in the latter group needed TPN, mainly due to poor food intake caused by pain/discomfort in the pharynx. However, in the allogeneic group, only busulfan-fludarabine conditioning and gender were predictive factors for body weight decrease. Fludarabine

has been used in association with busulfan for reducing the toxicity and improving HSCT outcomes (14). Despite of this, significant catabolism and reduction in nutrient absorption can be expected after this regimen because of the intense aggression to the gastrointestinal tract (15,16).Gender was also other independent predictive factor for body weight loss in the allogeneic transplantation. In this study, men had more loss of body weight than women, but we found no other association explaining this result. All variables related to gastrointestinal mucositis as well as length of neutropenia, BMI distribution and exposure to chemotherapy and immunosuppressive drugs were similar between male and female. Other study reported a worse nutritional status in men than in women at the moment of discharge from a HSCT transplantation center, and the authors found no explanation for such a finding (17). More studies are necessary for understanding the effect of gender on nutritional status during allogeneic HSCT.

Autologous and allogeneic transplantations showed different predictive factors that explained the variations on body weight during HSCT. Higher incidence of toxicity, higher morbidity and poor nutritional conditions are more commonly found in allogeneic than in autologous patients (17). In fact, in this study, allogeneic patients had a median of weight loss higher than that of autologous patients, as well as longer duration and worse severity of mucositis. Therefore, we have decided to maintain the two types of transplantation in two independent groups.

Body weight gain during HSCT can also be a sign of poor nutritional status, mainly resulting from nitrogen imbalance, hypoalbuminemia and electrolyte disturbances, leading to fluid accumulation in the body (18,19). Body weight gain in HSCT is also associated with hepatic veno-occlusive disease (20), renal insufficiency (21), engraftment syndrome (22), and capillary leak syndrome in the early phase of the transplantation (23). Most of these disorders are accompanied by an increase in the levels of inflammatory protein, such as IL-6 and C-reactive protein, which have also been associated with body weight gain (19). In this study, we found that the number of days of pain/discomfort in the oral cavity was an independent predictive factor for body weight gain in the autologous group. We did not find any direct explanation for this result. We believe that symptoms in the oral cavity resulting not only from OM, but also from gustatory and salivary alterations, were consequence of a systemic inflammatory condition derived from the process of conditioning and marrow engraftment. In addition, we found a significant association between hyponatremia and body weight gain in autologous group. Therefore, body weight gain may be due to nutritional/ electrolyte deficiencies associated with endothelial dysfunction involving an inflammatory insult, and the symptoms in the oral cavity were more a clinical manifestation of this complex condition, thus having an indirect association.

Although the OM severity was low and not associated with body weight loss in this study, in the autologous group the duration of OM impacted significantly the OS. Other study on autologous HSCT and conditioning regimen with busulfan, cyclophosphamide, and etoposide showed that severe OM reduced significantly the OS (24). In this study, duration of OM longer than 3 days reduced significantly the OS in autologous HSCT patients, but the real causes should be elucidated in further studies.

Body weight loss had a significant negative impact on the OS only in the allogeneic HSCT. In this group, 35.2% of the patients showed a body weight loss $\geq$5% in relation to the baseline. However, when we analyzed the OS curves considering this critical loss percentage, there were no significant differences between the OS probabilities. The rate of body weight loss that impacts negatively OS should be better determined in allogeneic patients. This result is probably related to the duration of diarrhea, a variable also having an impact on OS. We did not find any study showing this relationship, and further investigation should be conducted to elucidate it.

This retrospective study has limitations, including the absence of analyses of nutritional markers/parameters that could better explain the body weight variations, the relative low number of eligible patients in each group and the poor description of other important variables that may be related to nutritional disturbances, such as presence of comorbidities and incidence of acute GVHD. Therefore, the results described in this study should be considered with caution as they probably reflect a particular context of our HSCT center.

In summary, OM was not a risk factor for body weight loss during HSCT, but interfered with other factors related to body weight gain and had a negative impact on OS in autologous HSCT patients. Intestinal mucositis explained partially the body weight loss in some patients, and had a negative impact on OS in allogeneic transplantation. Further studies analyzing other variables besides the toxicity in the digestive tract are necessary to better explain the risk of nutritional disturbances during HSCT.

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