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Nutritional assessment as predictor of complications after hematopoietic stem cell transplantation



Marcela Espinoza, Javiera Perelli, Roberto Olmos, Pablo Bertin, Verónica Jara, Pablo Ramírez*

School of Medicine, Pontificia Universidad Católica de Chile (UC), Santiago, Chile

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ABSTRACT

Introduction: Nutritional support is pivotal in patients submitted to hematopoietic stem cell transplantation. Nutritional status has been associated with time of engraftment and infection rates. In order to evaluate the association between nutritional parameters and clinical outcomes after transplantation a cohort of transplant patients was retrospectively evaluated.

Methods: All 50 patients transplanted between 2011 and 2014 were included. The nutritional status before transplantation, ten days after transplantation and before discharge was assessed including anthropometry, body mass index, albumin, prealbumin and total urinary nitrogen.

Results: The median follow-up time was 41 months and the median age of patients was 41 years. Thirty-two underwent allogeneic and 18 autologous transplants. Diagnoses included acute leukemias ($n=27$), lymphoma ($n=7$), multiple myeloma ($n=13$), and aplastic anemia ($n=3$). Thirty-seven patients developed mucositis (three Grade 1, 15 Grade 2, 18 Grade 3 and one Grade 4), and twenty-two allogeneic, and five autologous transplant patients required total parenteral nutrition. Albumin and total urinary nitrogen were associated with length of hospital stay and platelet and neutrophil engraftment. None of the nutritional parameters evaluated were associated with overall survival. Non-relapse mortality was 14% and overall survival was 79% at 41 months of follow-up.

Conclusions: After hematopoietic stem cell transplantation, high catabolism was associated with longer length of hospital stay, the need of total parenteral nutrition and platelet and neutrophil engraftment times. Nutritional parameters were not associated with overall survival.

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* Corresponding author at: Departamento de Hematología y Oncología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Lira 85, Piso 4, Santiago, Chile.

E-mail address: pramirez@med.puc.cl (P. Ramírez).

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Introduction

Nutritional support is one of the most important issues in the management of patients who undergo hematopoietic stem cell transplantation (HSCT).^{1,2} Many factors induce changes in the metabolism during HSCT³ including high-dose chemotherapy and total body irradiation, mucositis with painful ulcers, diminished ingestion, nausea, vomiting and diarrhea.² Allogeneic HSCT (allo-HSCT) usually produces the greatest changes in body composition and muscle metabolism, infections and acute graft-versus-host disease (aGVHD).^{4,5}

Malnutrition has been identified as a major challenge in HSCT. Furthermore in malnourished (under and overweight) patients, studies have shown a higher risk of complications: changes in the body composition resulting in electrolyte imbalance and impairment of the immune system (both associated with longer engraftment time) and most of all, higher non-relapse mortality rates in the immediate post-transplant period.⁶⁻⁹

Energy requirements after transplantation usually increase by 30-50%, which is why nutritional support has been suggested as a contributing factor to an improved engraftment time and lower risk of infection during the neutropenic stage.⁹⁻¹¹ Parenteral nutrition is supportive care, which maintains the nutritional status of patients during the transplant process.

There are now many nutritional parameters available in the nutritional assessments of cancer patients and specifically HSCT patients. This paper presents the impact of pre-HSCT and post-HSCT biochemical and anthropometric evaluations on the clinical outcomes of HSCT. Thus, the aim of this study was to identify any associations between several nutritional parameters and the incidence of gastrointestinal and hepatic aGVHD, infectious complications, length of hospital stay, delayed neutrophil or platelet engraftment and overall survival (OS).

Methods

Patients

All patients who underwent autologous HSCT (auto-HSCT) and allo-HSCT between 2011 and 2014 at the Pontificia Universidad Católica de Chile were included in this study. Data were collected from the electronic and paper charts as well as the HSCT program database. The study was approved by the institutional review board.

Transplant procedure

After the decision to transplant had been made, patients underwent a number of evaluations to determine their suitability for transplantation and, when apt, auto-HSCT or allo-HSCT was performed. Conditioning regimens for the HSCT are shown in Table 1.

In sibling and matched unrelated HSCT, prophylaxis for graft-versus-host disease (GVHD) was made with cyclosporine

Table 1 – Patient characteristics.

Gender – n (%)	
Male	33 (66)
Female	17 (34)
Median Age – years (range)	
	41 (17–67)
Diagnosis – n (%)	
Acute leukemia	26 (52)
Myelodysplastic syndrome	1 (2)
Lymphoma	7 (14)
Myeloma	13 (26)
Aplastic anemia	3 (6)
Average length of stay – days (range)	
	32 (19–109)
Type of transplant – n (%)	
Autologous	18 (36)
Allogeneic	32 (64)
Related	20 (63)
Unrelated	9 (28)
Cord	3 (9)
Conditioning – n (%)	
Myeloablative	42 (84)
Reduced intensity	8 (16)

and methotrexate or tacrolimus and methotrexate. In cord blood HSCT, GVHD prophylaxis was made with cyclosporine and mycophenolate mofetil.

Prophylaxis against infectious diseases for all the patients included levofloxacin (500 mg q.d.) starting on Day –1 until neutrophil recovery or febrile neutropenia, acyclovir (400 mg t.i.d.) starting on Day –1 until Day +365, fluconazole (200 mg q.d.) starting on Day –1 until Day +100 and sulfamethoxazole trimethoprim (q.d. 3 times a week) starting with neutrophil recovery until Day +365. Similarly, all patients were kept in isolated rooms with high efficiency particulate air filters and positive pressure during the neutropenic phase of the transplant. Patients were given a neutropenic diet and received intravenous filgrastim 300 µg starting on Day +5 until neutrophil engraftment.

Nutritional evaluation

A nutritional evaluation was conducted at the time of HSCT, ten days after HSCT and before patient discharge. Pre-transplant assessments included body mass index (BMI), anthropometry, and measurements of the albumin, prealbumin and total urinary nitrogen (TUN) levels. Clinical and laboratory variables including cell counts, hematological condition and conditioning regimens were recorded.

Post-transplant assessment included BMI, albumin, prealbumin, TUN and type of nutritional support [oral, oral plus supplement, enteral nutrition or total parenteral nutrition (TPN)].

Grip strength was measured using a Jamar analogue hand dynamometer with participants seated in the upright position, their elbow by their side and flexed at right angles, with neutral wrist position. The best of three grip strength tests was calculated. This measurement was extrapolated to theoretical 85 percentile tables by gender and age.

Definitions

BMI was calculated according to Hannan.¹² BMI < 20 kg/m² was considered underweight, between 20–25 kg/m² normal, 25–30 kg/m² overweight and >30 kg/m² obese. Prealbumin was quantified using the nephelometry method with normal values between 18 and 38 mg/dL, albumin was quantified using the colorimetric method with normal values between 3.5 and 5.0 mg/dL and 24-h TUN was assessed using the Kjeldahl method. Patients who required TPN were prescribed for a specific number of days. Mucositis (Grade 1 to 4) and infectious complications (Grade 1 to 5) were graded according to the National Health Institute and Common Terminology Criteria for Adverse Events v 4.03.¹³ Acute GVHD (hepatic and intestinal) was graded according to the International Bone Marrow Transplant Registry (IBMTR) scale.¹⁴ Time to neutrophil and platelet engraftment was defined according to standard definitions: neutrophil count >500 cells/ μ L for three consecutive days and platelet count >50,000 cells/ μ L for seven consecutive days without the patient requiring transfusions.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (Version 20; Chicago, IL, USA). Results are presented as mean values. The ANOVA test was used to compare three mean values of the evaluations performed before the transplant, ten days after transplant and at discharge and the t-test to compare two

means (auto-HSCT vs. allo-HSCT). Multivariate analysis used the Spearman coefficient. BMI, dynamometry, albumin, prealbumin, TUN, triglycerides, time to platelet and neutrophil engraftment, length of hospital stay and OS were considered continuous variables and the need of TPN, aGVHD and presence of mucositis, categorical variables. The Cox Proportional Hazards test was used to estimate the OS.¹⁵ OS and non-relapse mortality were analyzed by the Kaplan–Meier method. Statistical significance was set for p-values <0.05.

Results

Characteristics of patients and the hematopoietic stem cell transplantation procedure

Fifty patients transplanted between 2011 and 2014 were analyzed. Patient characteristics are shown in Table 1. Thirty-three (66%) were men and seventeen (34%) were women. The average age was 41 years (range: 17–67 years). In all, 32 allo-HSCT and 18 auto-HSCT were performed. Indications for HSCT were acute leukemias in 26 patients (52%), multiple myeloma in 13 (26%), lymphoma in seven (14%), severe aplastic anemia in three (6%) and myelodysplastic syndrome in one (2%). The average length of hospital stay was 32 days (range: 19–109 days).

Conditioning regimens (Table 2) were myeloablative in 42 cases (84%) and reduced intensity in eight cases (16%). The median follow-up time was 41 months (range: 2–83 years).

Table 2 – Conditioning regimens.

Myeloablative regimen	Type of HSCT	n (%)	Indication	Therapy	Dose	Days before HSCT
Cy/TBI	allo	21 (42)	Acute leukemia	TBI	1320 cGy total	5–2
Mel 200	auto	12 (24)	Myeloma	Cy	60 mg/kg	7–6
BEC	auto	4 (8)	Lymphoma	Melphalan	200 mg/m ²	2
				Carmustine	300 mg/m ²	6
				Etoposide	200 mg/m ²	6–4
					twice a day	
				Cy	60 mg/kg	6–3
Cy/ATG/MP	allo	2 (4)	Aplastic anemia	Cy	50 mg/kg	5–2
				ATG	2.5 mg/kg	4–1
				MP	250 mg/m ²	4–1
					twice a day	
Flu/Cy/TBI	allo/cord	3 (6)	acute leukemia	Fludarabine	25 mg/m ²	8–6
				Cy	60 mg/kg	7–6
				TBI	1320 cGy total	4–1
Reduced intensity regimens	Type of HSCT	n (%)	Indication	Therapy	Dose	Days before HCT
Flu/Mel	allo	2 (4)	Lymphoma	Fludarabine	30 mg/m ²	8–4
				Melphalan	70 mg/m ²	3–2
Flu/Cy/TBI	allo	5 (10)	Acute Leukemia	Fludarabine	40 mg/m ²	6–2
				Cy	50 mg/kg	6
				TBI	200 cGy	1
Mel 140	auto	1 (2)	Myeloma	Melphalan	140 mg/m ²	2

HSCT: hematopoietic stem cell transplantation; allo: allogeneic; auto: autologous; TBI: total body irradiation; Cy: cyclophosphamide; ATG: anti-thymocyte globulin; MP: methylprednisolone.

Table 3 – Nutritional assessment comparing allogeneic and autologous hematopoietic stem cell transplantation at different time points.

Parameter	Allo Mean (range)	Auto Mean (range)	p-Value
<i>At admission</i>			
BMI – kg/m ²	27.0 (22.7–31.3)	27.0 (23.8–30.2)	0.99
DNM – kg	74.0 (48.1–99.9)	95.2 (66.9–123.5)	0.053
Albumin – mg/dL	4.12 (3.8–4.4)	4.12 (3.8–4.4)	0.99
Prealbumin – mg/dL	25.37 (19.8–30.9)	25.22 (18.9–31.5)	0.93
TUN – g/24 h	18.77 (9.9–27.5)	19.43 (13.2–25.6)	0.80
TG – mg/dL	171 (68–274)	103 (28–152)	0.07
<i>Ten days after transplant</i>			
BMI – kg/m ²	19.04 (8.0–30.0)	15.33 (3.7–26.8)	0.27
DNM – kg	72.09 (51.0–93.1)	70.85 (50.0–91.6)	0.89
Albumin – mg/dL	3.23 (2.2–3.9)	3.42 (2.9–3.9)	0.08
Prealbumin – mg/dL	17.74 (9.6–25.8)	19.99 (11.1–28.7)	0.29
TUN – g/24 h	21.63 (14.6–28.6)	22.96 (15.2–30.7)	0.56
TG – mg/dL	263 (138–387)	111 (49–173)	0.014
<i>Before discharge</i>			
BMI – kg/m ²	N/D	N/D	
DNM – kg	N/D	N/D	
Albumin – mg/dL	3.43 (2.9–3.9)	3.53 (3.1–3.9)	0.52
Prealbumin – mg/dL	23.21 (13.7–32.6)	21.26 (15.6–26.8)	0.54
TUN – g/24 h	23.25 (12.9–33.5)	21.21 (14.5–27.9)	0.56
TG – mg/dL	331 (148–514)	N/D	

Allo: allogeneic; Auto: autologous; BMI: body mass index; DNM: dynamometry; TUN: total Urinary Nitrogen; TG: triglycerides; N/D: no data available.

Nutritional status before and after hematopoietic stem cell transplantation

At admission for HSCT, there were no significant differences regarding nutritional parameters between the groups of allo-HSCT and auto-HSCT patients (Table 3). After transplantation only the triglycerides levels were significantly higher in the allo-HSCT Group compared to auto-HSCT Group. The other parameters were similar between both groups (Table 3).

On combining the HSCT groups, there were significant reductions in the BMI, and prealbumin and albumin levels in the post-transplant period compared to the pre-transplant period. Triglyceride levels were significantly higher in the post-transplant assessment. No differences in TUN and dynamometry were found between the three evaluations (Table 4).

Considering the type of HSCT, albumin levels decreased significantly in both the allo-HSCT and auto-HSCT Groups after transplantation. However, the reduction in prealbumin,

as well as the increase in triglyceride levels, were only significant in the allo-HSCT group, while a significant drop in BMI was only seen in the auto-HSCT group (Table 5).

Post-transplant complications

Considering all patients, 37 (74%) developed mucositis [allo-HSCT: n = 24 (75%) and auto-HSCT: n = 13 (72%); p-value <0.05]. According to the degree of mucositis three patients had Grade 1, 15 patients Grade 2, 18 patients Grade 3 and one had Grade 4 (Figure 1). Of the 37 patients with mucositis, 27 (73%) required TPN [allo-HSCT: n = 22 (81%) and auto-HSCT: n = 5 (19%)] and 10 (27%) some other kind of nutritional support. According to the type of transplant, 28% (5/18) of auto-HSCT and 69% (22/32) of allo-HSCT patients required TPN. Figure 2 shows the distribution of nutritional support in the different groups. Eight patients without mucositis also required TPN because of severe nausea and vomiting.

Table 4 – Nutritional assessment before transplant, 10 days after transplant and at discharge.

Parameter	Before transplant Mean (range)	Day +10 Mean (range)	Before discharge Mean (range)	p-Value
BMI (kg/m ²)	26.9 (20.9–34.6)	26.1 (20.0–34.7)	N/D	<0.01
DNM (kg)	79.7 (24.3–142.0)	72.5 (33.0–109.0)	N/D	0.9
Albumin (mg/dL)	4.1 (3.5–4.9)	3.3 (2.2–4.0)	3.5 (2.0–4.4)	<0.01
Pre-albumin (mg/dL)	25.4 (14.6–35.5)	18 (7.2–34.5)	21.9 (10.9–50.4)	<0.01
TUN g/24 h	18.2 (4.0–44.6)	22.1 (9.9–41.4)	22.6 (9.0–50.0)	0.1
TG (mg/dL)	148.7 (40–465)	235 (46–557)	324.8 (96–863)	<0.01

BMI: body mass index; DNM: dynamometry; TUN: total urinary nitrogen; TG: triglycerides; N/D: no data available.

Table 5 – Nutritional assessment before and after hematopoietic stem cell transplantation according to the type of transplantation.

Parameter	Before	Day +10	At discharge	p-Value
Allogeneic				
BMI (kg/m ²)	26.6	25.8	N/D	0.13
DNM (kg)	76.1	74.5	N/D	0.85
Albumin (mg/dL)	4.1	3.25	3.4	<0.01
Pre-albumin (mg/dL)	25.6	15.7	23.2	0.01
TUN g/24 h	18.9	21.5	23.2	0.19
TG (mg/dL)	172.5	255.5	331.8	<0.05
Autologous				
BMI (kg/m ²)	27.3	26.3	N/D	<0.05
DNM (kg)	89.7	69	N/D	0.6
Albumin (mg/dL)	4.16	3.4	3.5	<0.01
Pre-albumin (mg/dL)	25.2	20.5	21.2	0.054
TUN g/24 h	17.2	23.9	21.2	0.39
TG (mg/dL)	111	103	272.5	0.072

Results shown as means.

BMI: body mass index; DNM: dynamometry 85% standard for age and gender; TUN: total urinary nitrogen; TG: triglycerides; N/D: no data available.

Considering the 32 allo-HSCT patients, nine (28%) developed intestinal aGVHD (five patients submitted to unrelated HSCT and four to related HSCT) and 23 (72%) did not develop intestinal aGVHD. The severity was Grade II-IV in five (56%) and Grade III-IV in four (44%). The average time from HSCT to aGVHD was 34 days (range: 16–80 days). Overall, 69% (22/32) of the allo-HSCT patients required TPN. All of the patients who developed intestinal aGVHD required TPN and 57% (13/23) of the patients without intestinal GVHD required TPN, mainly due to anorexia.

The 41-month OS was 79% (auto-HSCT: 81%; allo-HSCT: 75%; *p*-value=NS). The non-relapse mortality rate (2 auto-HSCT and 4 allo-HSCT) was 12% at 41 months (11% auto-HSCT and 13% allo-HSCT; *p*-value=NS).

Multivariate analysis

In the multivariate analysis, none of the pre-HSCT nutritional parameters was associated with transplant outcomes.

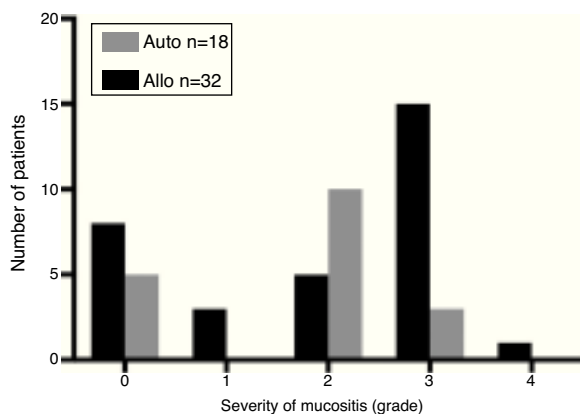


Figure 1 – Distribution of mucositis according to grade and type of hematopoietic stem cell transplantation.
auto: autologous hematopoietic stem cell transplantation;
allo: allogeneic hematopoietic stem cell transplantation.

However, several post-HSCT nutritional parameters were statistically associated with transplant outcomes. Specifically, ten days after transplant, albumin was associated with length of hospital stay and time to platelet engraftment; TUN was correlated with time to platelet engraftment and days of TPN with length of hospital stay, time to neutrophil engraftment and time to platelet engraftment. Only TUN was associated with time to neutrophil engraftment in the pre-discharge evaluation. Finally, OS was not affected by any variable in the multivariate analysis (Table 6).

Discussion

This is the first study from Chile to report on nutritional support in HSCT patients. Nutritional impairment is significant after transplantation¹⁶ and is associated with worse outcomes.¹⁷ Malnourishment increases the risk of death,

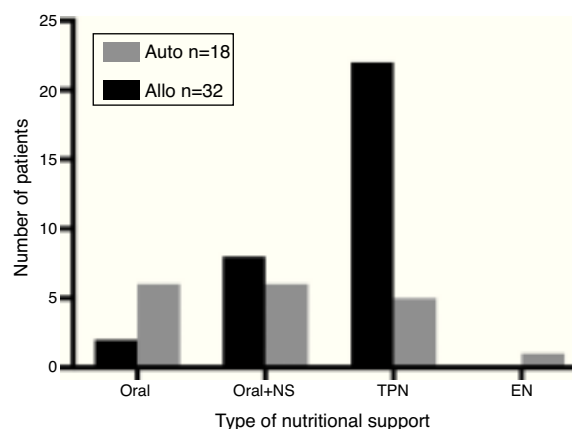


Figure 2 – Type of nutritional support required.
auto: autologous hematopoietic stem cell transplantation;
allo: allogeneic hematopoietic stem cell transplantation;
NS: nutritional supplements; TPN: total parenteral nutrition; EN: enteral nutrition.

Table 6 – Significance (p-values) by multivariate analysis of factors potentially associated with complications of hematopoietic stem cell transplantation.

Factor	HCT complications					
	aGVHD	LOS	IC	TNE	TPE	OS
BMI before HSCT	0.444	0.277	0.326	0.25	0.249	0.925
Albumin after HSCT	0.738	0.463	0.871	0.36	0.322	0.689
Pre-albumin before HSCT	0.765	0.199	0.639	0.128	0.054	0.819
TUN before HSCT	0.625	0.052	0.786	0.397	0.171	0.613
BMI after HSCT	0.057	0.149	0.995	0.342	0.303	0.863
Albumin after HSCT	0.152	0.012	0.835	0.271	0.015	0.822
Pre-albumin after HSCT	0.507	0.062	0.797	0.167	0.065	0.391
TUN after HSCT	0.945	0.13	0.503	0.087	0.026	0.932
Days of TPN	0.834	0.001	0.062	0.002	0.001	0.159
Albumin before d/c	0.295	0.125	0.653	0.161	0.193	0.358
Pre-albumin before d/c	0.073	0.827	0.69	0.350	0.309	0.297
TUN before d/c	0.165	0.304	0.084	0.029	0.344	0.556

aGVHD: acute graft versus host disease; LOS: length of hospital stay; IC: infectious complications; TNE: time to neutrophil engraftment; TPE: time to platelet engraftment; OS: overall survival; HSCT: hematopoietic stem cell transplantation; BMI: body Mass Index; TUN: total urinary nitrogen; TPN: total parenteral nutrition; d/c: discharge.

mucositis, aGVHD and infectious complications in patients submitted to HSCT.^{9,17,18}

Several studies have addressed the topic of specific nutritional parameters in HSCT, with discordant findings. Schulte et al., without demonstrating any association between BMI and transplant complications, reported a significant decrease in BMI after HSCT, which reverted one year after transplantation.¹⁰ Other authors have identified low pre-transplant BMI as an independent risk factor for mortality.¹⁹⁻²² Urbain et al. showed that aGVHD and anorexia during transplant were associated with significant reductions in BMI in an allo-HSCT cohort.⁹ This study found an overall drop in BMI after HSCT, with statistical significance only for the auto-HSCT Group.

When considering other parameters, the study of Schulte et al. showed a significant reduction in prealbumin levels at Day +14 and +28 after HSCT.¹⁰ In the current study, this reduction was noticed even before, at Day +10, and persisted until patient discharge. Albumin levels showed a significant reduction in the same period irrespective of the type of HSCT, which correlated with both a longer length of hospital stay and platelet engraftment time.

The differences found between allo-HSCT and auto-HSCT may suggest a higher degree of catabolism in the allo-HSCT setting. Specifically, this study observed that earlier in the course of HSCT, the TUN levels tend to be higher after auto-HSCT compared to allo-HSCT. However, before discharge TUN was higher, albeit not significantly, in the allo-HSCT Group than the auto-HSCT Group. Moreover, albumin levels can change in acute renal failure and during the use of transfusion support, which is very common in this kind of patient.^{23,24} A study of Underzo et al.²⁵ showed that after TPN, albumin levels after HSCT did not change over one week but prealbumin levels did, which makes this variable a more accurate parameter for diet and nutritional assessments. Together with prealbumin, research has shown decreases of other parameters after HSCT such as transferrin and retinol binding protein that might predict malnutrition in allo-HSCT and auto-HSCT.²⁶ In

this study, higher TUN levels were associated with slower neutrophil and platelet engraftment. This may suggest that higher TUN levels are a surrogate of more severe infectious complications, which could be associated to delayed engraftment time. Research failed to show an association between nutritional support and time to neutrophil engraftment.^{27,28} However, a study by Habjibabae et al. suggested that BMI, but not TUN, was inversely correlated with the neutrophil engraftment time.²⁹

When considering complications after HSCT, the incidence of mucositis reported in this study was 74%, similar to the incidence of 70% reported in the literature.³⁰ Days of TPN correlated with the length of hospital stay and time to platelet and neutrophil engraftment.

None of the nutritional factors analyzed at different time points including BMI, albumin, prealbumin, TUN and TPN, were associated with OS in this study, and survival rates were similar between allo-HSCT and auto-HSCT patients, possibly due to the early nutritional support provided to all patients and the small number of patients analyzed which precluded statistically significant differences. The high mortality rate in auto-HSCT patients is possibly associated with the low number of this type of patients included in this study.

This research was unable to demonstrate any association between TPN and a higher rate of intestinal aGVHD. However, there are possible explanations for the association between mucositis, aGVHD and TPN that have been suggested before. Mucosa-associated lymphoid tissue (MALT), while normally acting as an immunological barrier, may suffer severe damage during conditioning for HSCT. The subsequent bacterial and toxin translocation may act as a potent inflammatory stimulus for the development of acute aGVHD.^{31,32} As shown by Mattsson et al., the oral feeding route seems to have a protective role against the development of GVHD.³³ In their study of 231 patients submitted to myeloablative conditioning, these authors found a cumulative incidence of 39% of Grade II to IV aGVHD in patients who did not receive any oral nutrition for nine or more days (13 patients). However, in 144 patients

with oral intake, there was a cumulative incidence of only 7% of aGVHD. In the current study, all of the patients with gastrointestinal aGVHD required TPN and less than half of the patients without intestinal aGVHD required TPN, mainly for anorexia. However, due to the small number of patients with aGVHD no conclusions can be reached regarding the association between aGVHD and nutritional support. TPN has been associated with intestinal atrophy and enhanced expression of interferon gamma, while local levels of cytokines that protect from GVHD, such as IL-4 and IL-10, usually show a significant decrease in patients using this type of nutritional support.³⁴ Furthermore, many studies in critical patients have consistently shown a higher incidence of infectious complications in TPN versus oral/enteral nutrition, which may be another possible link between the feeding route and complications such as mucositis and aGVHD.³⁵

In the current series, the majority of patients requiring nutritional support received TPN. Controversy exists on the best nutritional support after transplantation. A study by Szeluga et al.³⁶ showed that compared to oral nutrition, TPN was not associated with OS or hematopoietic recovery and length of hospitalization but was associated with a longer use of diuretics, more hyperglycemia and more catheter-related complications. Recent studies have suggested that early enteral support could be associated with better outcomes compared to TPN, including faster engraftment times.^{37,38} However up to 90% of the patients undergoing myeloablative allo-HSCT will still receive TPN.³⁹ In the current series, one-third of the auto-HSCT and two thirds of the allo-HSCT received TPN.

The main limitation of this study is its retrospective nature, which precludes the investigation of causative associations between variables and outcomes. However, this study identifies some variables that should be considered to predict the evolution of patients during the acute phases of HSCT, and to develop more precise ways to assess nutritional status.

Conclusions

This study shows that allo-HSCT and auto-HSCT patients become significantly hypercatabolic during the acute phase of transplants and the majority will develop mucositis requiring nutritional support early in the course of the transplant process. Of all the variables analyzed, albumin and TUN were associated with clinical outcomes. OS was not associated with any nutritional parameter.

Since this is not a comparative study, we cannot predict the outcome of patients without appropriate nutritional support. However due to the frequency and severity of mucositis and the degree of catabolism it seems reasonable to deliver appropriate nutritional support although the best source is still under study, with studies suggesting advantages of enteral nutrition over TPN.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

1. Mousavi M, Hayatshahi A, Sarayani A, Hadjibabaie M, Javadi M, Torkamandi H, et al. Impact of clinical pharmacist-based parenteral nutrition service for bone marrow transplantation patients: a randomized clinical trial. *Support Care Cancer*. 2013;21(12):3441-8.
2. Rzepecki P, Barzal J, Oborska S. Blood and marrow transplantation and nutritional support. *Support Care Cancer*. 2010;18 Suppl. 2:S57-65.
3. Thompson JL, Duffy J. Nutrition support challenges in hematopoietic stem cell transplant patients. *Nutr Clin Pract*. 2008;23(5):533-46.
4. Hickson RC, Marone JR. Exercise and inhibition of glucocorticoid-induced muscle atrophy. *Exerc Sport Sci Rev*. 1993;21:135-67.
5. LaPier TK. Glucocorticoid-induced muscle atrophy. The role of exercise in treatment and prevention. *J Cardiopulm Rehabil*. 1997;17(2):76-84.
6. Faghihi T, Irvani M, Shamshiri AR, Hadjibabaie M, Mousavi SA, Alimoghaddam K, et al. Serum electrolyte changes at engraftment time in patients undergoing allogeneic hematopoietic stem cell transplantation. *Ann Transplant*. 2009;14(3):51-7.
7. Hacker ED, Ferrans CE. Quality of life immediately after peripheral blood stem cell transplantation. *Cancer Nurs*. 2003;26(4):312-22.
8. McDiarmid S. Nutritional support of the patient receiving high-dose therapy with hematopoietic stem cell support. *Can Oncol Nurs J*. 2002;12(Spring (2)):102-15.
9. Urbain P, Birlinger J, Lambert C, Finke J, Bertz H, Biesalski HK. Longitudinal follow-up of nutritional status and its influencing factors in adults undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2013;48(3):446-51.
10. Schulte C, Reinhardt W, Beelen D, Mann K, Schaefer U. Low T3-syndrome and nutritional status as prognostic factors in patients undergoing bone marrow transplantation. *Bone Marrow Transplant*. 1998;22(12):1171-8.
11. Lipkin AC, Lenssen P, Dickson BJ. Nutrition issues in hematopoietic stem cell transplantation: state of the art. *Nutr Clin Pract*. 2005;20(August (4)):423-39.
12. Hannan WJ, Wrate RM, Cowen SJ, Freeman CP. Body mass index as an estimate of body fat. *Int J Eat Disord*. 1995;18(1):91-7.
13. Bruner DW, Hanisch LJ, Reeve BB, Trotti AM, Schrag D, Sit L, et al. Stakeholder perspectives on implementing the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Transl Behav Med*. 2011;1(1):110-22.
14. Rowlings PA, Przepiorka D, Klein JP, Gale RP, Passweg JR, Henslee-Downey PJ, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *Br J Haematol*. 1997;97(4):855-64.
15. Cox C. Multinomial regression models based on continuation ratios. *Stat Med*. 1988;7(3):435-41.
16. Walrath M, Bacon C, Foley S, Fung HC. Gastrointestinal side effects and adequacy of enteral intake in hematopoietic stem cell transplant patients. *Nutr Clin Pract*. 2015;30(2):305-10.

17. Arends J, Zuercher G, Dossett A, Fietkau R, Hug M, Schmid I, et al. Non-surgical oncology – Guidelines on Parenteral Nutrition, Chapter 19. *Ger Med Sci*. 2009;7:Doc09.
18. Rodgers C, Walsh T. Nutritional issues in adolescents after bone marrow transplant: a literature review. *J Pediatr Oncol Nurs*. 2008;25(5):254–64.
19. Fleming DR, Rayens MK, Garrison J. Impact of obesity on allogeneic stem cell transplant patients: a matched case–controlled study. *Am J Med*. 1997;102(3):265–8.
20. Le Blanc K, Ringden O, Remberger M. A low body mass index is correlated with poor survival after allogeneic stem cell transplantation. *Haematologica*. 2003;88(9):1044–52.
21. Lenssen P, Sherry ME, Cheney CL, Nims JW, Sullivan KM, Stern JM, et al. Prevalence of nutrition-related problems among long-term survivors of allogeneic marrow transplantation. *J Am Diet Assoc*. 1990;90(6):835–42.
22. Nikolousis E, Nagra S, Paneesha S, Delgado J, Holder K, Bratby L, et al. Allogeneic transplant outcomes are not affected by body mass index (BMI) in patients with haematological malignancies. *Ann Hematol*. 2010;89(11):1141–5.
23. Bernstein LH, Leukhardt-Fairfield CJ, Pleban W, Rudolph R. Usefulness of data on albumin and prealbumin concentrations in determining effectiveness of nutritional support. *Clin Chem*. 1989;35(2):271–4.
24. Nitenberg G, Raynard B. Nutritional support of the cancer patient: issues and dilemmas. *Crit Rev Oncol Hematol*. 2000;34(3):137–68.
25. Uderzo C, Rovelli A, Bonomi M, Fomia L, Pirovano L, Masera G. Total parenteral nutrition and nutritional assessment and leukaemic children undergoing bone marrow transplantation. *Eur J Cancer*. 1991;27(6):758–62.
26. Rzepecki P, Barzal J, Sarosiek T, Szczylik C. Biochemical indices for the assessment of nutritional status during hematopoietic stem cell transplantation: are they worth using? A single center experience. *Bone Marrow Transplant*. 2007;40(6):567–72.
27. Ferreira EE, Guerra DC, Baluz K, de Resende Furtado W, da Silva Bouzas LF. Nutritional status of patients submitted to transplantation of allogeneic hematopoietic stem cells: a retrospective study. *Rev Bras Hematol Hemoter*. 2014;36(6):414–9.
28. Sommacal HM, Gazal CH, Jochims AM, Beghetto M, Paz A, Silla LM, et al. Clinical impact of systematic nutritional care in adults submitted to allogeneic hematopoietic stem cell transplantation. *Rev Bras Hematol Hemoter*. 2012;34(5):334–8.
29. Hadjibabaie M, Iravani M, Taghizadeh M, Ataie-Jafari A, Shamshiri AR, Mousavi SA, et al. Evaluation of nutritional status in patients undergoing hematopoietic SCT. *Bone Marrow Transplant*. 2008;42(7):469–73.
30. Gabriel DA, Shea T, Olajida O, Serody JS, Comeau T. The effect of oral mucositis on morbidity and mortality in bone marrow transplant. *Semin Oncol*. 2003;30 6 Suppl. 18:76–83.
31. Hill GR, Ferrara JL. The primacy of the gastrointestinal tract as a target organ of acute graft-versus-host disease: rationale for the use of cytokine shields in allogeneic bone marrow transplantation. *Blood*. 2000;95(9):2754–9.
32. Horsley P, Bauer J, Gallagher B. Poor nutritional status prior to peripheral blood stem cell transplantation is associated with increased length of hospital stay. *Bone Marrow Transplant*. 2005;35(11):1113–6.
33. Mattsson J, Westin S, Edlund S, Remberger M. Poor oral nutrition after allogeneic stem cell transplantation correlates significantly with severe graft-versus-host disease. *Bone Marrow Transplant*. 2006;38(9):629–33.
34. Sigalet DL, Mackenzie SL, Hameed SM. Enteral nutrition and mucosal immunity: implications for feeding strategies in surgery and trauma. *Can J Surg*. 2004;47(2):109–16.
35. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition*. 2004;20(10):843–8.
36. Szeluga DJ, Stuart RK, Brookmeyer R, Utermohlen V, Santos GW. Nutritional support of bone marrow transplant recipients: a prospective, randomized clinical trial comparing total parenteral nutrition to an enteral feeding program. *Cancer Res*. 1987;47(12):3309–16.
37. Seguy D, Duhamel A, Rejeb MB, Gomez E, Buhl ND, Bruno B, et al. Better outcome of patients undergoing enteral tube feeding after myeloablative conditioning for allogeneic stem cell transplantation. *Transplantation*. 2012;94(3):287–94.
38. Guïèze R, Lemal R, Cabrespine A, Hermet E, Tournilhac O, Combal C, et al. Enteral versus parenteral nutritional support in allogeneic haematopoietic stem-cell transplantation. *Clin Nutr*. 2014;33(3):533–8.
39. Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M. ESPEN Guidelines on Parenteral Nutrition: non-surgical oncology. *Clin Nutr*. 2009;28(4):445–54.