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EVALUATION OF PLATELETS TRANSFUSION IN PATIENTS UNDERGOING HIGH DOSE CHEMOTHERAPY FOR BONE MARROW TRANSPLANTATION

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ABSTRACT

Introduction: Microvascular endothelial damage is a well-recognized complication of bone marrow transplantation (BMT) and the mechanisms of this disorder are still poorly understood. The objective of this scenario is to evaluate the relationship between inflammatory markers and other factors that influence platelet consumption and platelet transfusion yield, as well as the presence of embolic and / or vascular thrombotic events in patients submitted to high-dose chemotherapy conditioning for Bone marrow transplant.

Material and Methods: Prospective analysis of patients, including 25 patients who underwent autologous and allogenic BMT. The patients were evaluated in relation to previous radiotherapy, CD34 + cell count, period of neutropenia, body mass index (BMI), ferritin, reactive C protein (RCP), relating these factors to the number of platelet transfusions, platelet refractoriness and vascular events such as sinusoidal obstruction syndrome (SOS) and bone marrow grafting syndrome.

Results: Only BMI> 25 Kg / m2 of the studied variables presented a statistically significant value (p = 0.003) in relation to the lower need for transfusion of platelet concentrate. For platelet refractoriness and / or vascular events none of the variables was statistically significant. The conditions found in the 3 cases of platelet refractoriness and in the 2 cases of vascular events have characteristics like those described in the literature.

Conclusion: Although the cause is unclear, we agree with data reported in the literature that patients with high BMI have a lower need for transfusion of platelets. Small sampling limits our comparisons and significant statistical inference; however, we cannot rule out the relevance of a descriptive analysis of the results, especially if we consider that each patient should be evaluated in an individualized way in clinical practice

Key words: BMT, endothelial lesion, platelet refractoriness, platelets transfusion

INTRODUCTION

Recent studies have shown that endothelial cells are much more than just vessel lining, these cells can control vascular smooth muscle tone by nitric oxide (NO), conserve different concentrations of procoagulants depending on the functional requirements and play an immunological role through interaction with circulating leukocytes.[1]

When endothelial function is disturbed, for instance, in cases of inflammatory conditions the endothelial surface rapidly converts from a non-thrombotic state to a procoagulant state, this change is due to desregulation of anticoagulant factors as well as activation of prothrombotic mediators. [2,3]

Some authors have demonstrated the interaction of several mechanisms in the association among obesity, metabolic syndrome, endothelial injury and platelet activation. Adipose tissue secretes proinflammatory cytokines such as: Interleukin-6 (IL-6) and Tumor Necrosis Factor Alpha (TNF-a), affecting both endothelial function and glucose metabolism. [4,5,6]

During hematopoietic stem cells transplant, endothelial cells can be activated and damaged by chemotherapy contained in the conditioning regimen, cytokines produced by injured cells, bacterial endotoxins translocated through the injured gastrointestinal tract, and by the complex process of graft versus host reaction. [7]

Microvascular endothelial dysfunction is a process recognized as a complication of bone marrow transplantation (BMT) and the mechanisms related to this disorder are still poorly understood. Transplant associated endothelial disorder is correlated to a group of complications such as, thrombotic microangiopathy, sinusoidal obstruction syndrome (SOS) and graft-versus-host disease (GVHD). [7]

Thrombocytopenia is frequently seen in the BMT scenario and it often requires platelets transfusions. In adult recipients of autologous hematopoietic stem cell transplantation (HSCT) randomized trials have demonstrated that they receiving platelet transfusion at the first sign of bleeding is better than prophylactically, principal for a prespecified subgroup of patients who undergoes autologous stem cell transplantation. [8,9]

The role of clinical knowledge related to variants linked to platelet recovery is important and assessment of risk factors associated with prolonged recovery include; use of radiation and its toxic effects on the bone marrow, a high mononuclear cell count in the receptor, fever and the presence of SOS. The variables related to the shortest time of thrombocytopenia are CD34 + counts and the early recovery of neutrophil counts. [7,10,11] Diagnosis of vascular complications in patients undergoing BMT is challenging, since there are so few markers of endothelial lesion available in clinical practice.[7]

In this context, the objectives of this article are to evaluate the relationship between inflammatory markers, available in clinical practices in our country, like serum ferritin and C-reactive protein (CRP) and other circumstances that influence platelet consumption and platelet transfusion increments, as well as the presence of thromboembolic and/or vascular events in patients submitted to high-dose chemotherapy-based regimes as conditioning for BMT.

METHOD:

A prospective analysis of patients was performed between March 2016 and October 2017 at the Bone Marrow Transplantation Service of the University Hospital of the Federal University of Juiz de Fora (HU-UFJF), where both autologous and allogeneic bone marrow transplantation were studied, being excluded those who did not present the necessary data to reach the evaluation of the objectives proposed or who did not sign the free and informed consent. This study was approved by the Human Research Ethics Committee of the HU-UFJF (CEP HU-UFJF), with its opinion nº. 1,466,443 and CAAE: 52091415.0.0000.5133.

Patients:

Patients who would be submitted to autologous and allogenic BMT of both sexes and any age were included in the study. The diagnosis of Bone Marrow Aplasia was an exclusion criterion since their characteristics being quite heterogeneous in relation to the rest of the studied patients, especially when observed the dependence of transfusion support in the pre BMT period. Patients were evaluated in relation to previous radiotherapy, CD34+ cell count, period of neutropenia, body mass index (BMI), ferritin, C-reactive protein (CRP), relating these factors to the number of platelet transfusions, platelet refractoriness and events such as SOS and Engraftment Syndrome following hematopoietic stem cell transplantation.

Sample collection:

To evaluate the inflammatory situation prior to infusion of high dose chemotherapy we collected: the CRP and ferritin at hospitalization, as well as considered the weight at the beginning of conditioning regimen to calculate the BMI. Five milliliters (ml) of whole blood were collected from each participant in an anticoagulated tube with ethylenediamine tetra acetic acid (EDTA) during the service collection routine. Quantification of CD34 + cells was performed on a double platform, cytometry was performed on the Fluorescence Activated Cell Analyzer, FACSCalibur, Becton Dickinson (BD) flow cytometer and cytometry analysis was performed on the Cell Quest analysis software according to the ISHAGE protocol (International Society of Hemotherapy and Graft Engineering).

Platelet increment:

For the calculation of platelet refractoriness, the CCI formula (correct count increment) was used, and those patients who presented post-transfusion 24-hour platelet yield (ICC-24 - collected between 18 and 24 hours post-transfusion) were considered, refractory less than 4500 platelets per ml in at least two transfusions, preferably consecutive, with compatible ABO platelets.[12]

$CCI = IP \times SC \times 10^{11} / n$

at where:

IP = increase in platelet count (x 10^9/L) (post-transfusion count - pre-transfusion count)

SC = body surface (m^2)

n = number of transfused platelets (x 10^{11}/L)

Serum ferritin was considered elevated when greater than 300 ng/mL, BMI altered when greater than 25 kg/m^2, CRP when greater than 2 mg/mL. For the diagnosis of SOS we used the modified Seattle Criteria: Presence before day 20 after BMT of two or more of the following: Bilirubin ≥ 2 mg /dl, Hepatomegaly, right upper quadrant pain, Ascites or unexplained weight gain of >2% baseline and the Engraftment Syndrome based on the Maiolino criteria, characterized by cutaneous rash, aseptic fever and pulmonary infiltrates or diarrhea 24 hours before or at the moment of grafting. [13]

Patients received irradiated platelets when the counts were less than 10,000 to 20,000 mm^3 platelets. One unit of platelet concentrate per 10 kg of patient weight was transfused per transfusion episode when random platelets were used, and single platelets donor apheresis collections were considered equivalent to 6 units of random platelets.

Data analysis:

After the assessment of platelets transfusion need in conjunction with the presence of thromboembolic events and platelet refractoriness, it was compared based on the values found in the relation with factors that could be related to a greater transfusion dependence and consequent increased life risk to the patients submitted to HSCT. The factors analyzed were radiotherapy, type of transplant (Autologous / Allogenic), preconditioning CD34 + cells, febrile neutropenia, days of neutropenia, BMI, use of two or more antibiotics, ferritin and RCP. The medians of platelets transfusions per transfusional episodes are considered as the most correct method to obtain an estimate of the consumption of Platelet Concentrate (PC), since a normal distribution between the groups was not found.

The analyzes were performed in the Statistical Package program for Social Science (SPSS) version 17.0. For the statistically significant values, the value of $p < 0.05$ was considered for the rejection of the null hypothesis

RESULTS

A total of 25 individuals with a median age of 38.8 years (14 to 61 years), 13 (52%) males and 12 (48%) females, 3 patients were excluded because they presented a diagnosis of bone marrow aplasia.

The characteristics of the evaluated patients are shown in Table 1. Of the evaluated variables, only BMI presented a statistically significant relationship ($p = 0.003$) with the number of transfused platelets concentrates, as an altered BMI (>25 Kg/m2) an indicative of lower platelets transfusions. For platelet refractoriness and/or vascular events none of the variables was statistically significant.

There was no difference between autologous and allogeneic BMT patients according to the number of transfused platelets concentrates (p=0,063), platelet refractoriness (p=0.13) and vascular events (p=0.13). Although there is a lower transfusion consumption of platelets in patients with high BMI (Table 2), the median of platelet concentrates per transfusion episodes of patients with normal BMI and those with high BMI was not statistically significant (High BMI x Normal BMI: 10.5 x 13 units of platelets, $p = 0.137$). (Graph 1)

Patients with platelet refractoriness are described in table 3. Vascular complications were present in 2 patients, one with SOS and another with Engraftment Syndrome, described in Table 4, where attention is drawn to the ferritin level of patient 1 and the number of CD34 + cells infused to the patient 2.

Discussion:

The results of this prospective cohort show a limitation of a study sample size. However, the understanding of the impact related to platelets transfusion events, refractoriness and certain pathologies with vascular characteristics are important.

Although the data postulate the lack of detection or inexistence of a significant relationship between inflammatory markers, platelet transfusion increment, as well as the presence of thromboembolic and /or vascular events, they are in agreement with preexisting data reported in the literature, where patients with high BMI have lower need of platelets transfusion.[14]

Although the cause is unclear, it can be inferred an association with the pro-inflammatory state, which is caused largely by IL-6 present in the circulation produced by adipose tissue. IL-6 acts strongly on the

proliferation of megakaryocyte progenitors and synergistically with thrombopoietin in the stimulation of megakaryopoiesis.[15] It is also observed a procoagulant state in obese and metabolic syndrome, which are characterized by high Tissue Factor levels, von Willebrand Factor, Factor VIII, Fibrinogen and platelet aggregation secondary to dyslipidemia and endothelial dysfunction present in subjects with high body weight.[5,16]

Patients undergoing BMT require serial platelet transfusions secondary to an intense and persistent thrombocytopenia, this situation is even more serious when the patient develops refractoriness to platelets transfusion. The frequency of patients with platelet refractoriness observed in the study (12%) was similar to those reported in the literature. Sherrill et al reported 13% of patients with platelet refractoriness otherwise others studies reported approximately half, ranging from 24% to 34%.[17]

Although the bleeding risk of patients receiving an allogenic transplantation was greater than those receiving an autologous transplantation[8], there was no impact in statistical analysis, between these two groups. This fact may occurred because there is a limitation of the small sample size could be explained by the reason that BMT is not a frequent procedure and performed in a single institution. The patient's characteristics at the refractory group demonstrates that exposure to a higher frequency of transfusion can lead to a platelet transfusion refractoriness, as in patient 3, who had a metallic heart valve and required full anticoagulation during the period of thrombocytopenia for this reason he was maintained with serial platelet transfusions in order to keep a platelet count around 50,000 mm^3.Other factors related to a worse post-transfusion platelet increament and platelet refractory, present in the study, which coincide with the literature were SOS, fever and the presence of splenomegaly. The increased spleen is documented as a factor of platelet refractoriness and lower interval between platelets transfusions.[18, 19]

In SOS, there is evidence that both thrombocytopenia and platelet refractoriness, probably related to disordered endothelial activation, are early markers of its presence. The low platelet increment of these patients may be related to endothelial lesion resulting from the chemotherapy program submitted to the patient with an increase in platelet adhesion to the damage endothelium, resulting in a leakage of platelets from the circulation.[17,20,21] Iron overloads is also associated with sinusoidal obstruction syndrome and ferritin levels greater than 1000 ng / dL in the pre-transplant period are an independent risk factor for this disease.[22] The results of our research do not corroborate the evidence related to high ferritin levels, as an independent risk at the pre-transplantation evaluation for vascular events, even though when we analyze the single SOS event, attention is drawn to the ferritin level of the patient in question, disproportionate to the sample. Although the single event is not significant in relation to the sample size, it presents a pattern like those described in the literature. [23, 24]

Engraftment Syndrome, the second vascular event diagnosed during the study period, presents a risk of pulmonary complications like transfusion-related lung injury. This syndrome often starts with fever and hypoxia at the time of leukocyte recovery and presents a possible and well-known correlation with the high number of infused CD34+ cells,[13, 25, 26] studies have shown that for a successful grafting the number of CD34+ cells is an important factor, with a dose of 3.5-5 x 10^6 cells/kg/weight being the optimal value. [11] The infusion of CD34+ > or = 5 x 10^6/kg, although it is related to a lower need for hemotherapy support, it raises the risk for Engraftment Syndrome,[13, 27] according to the only patient who evolved with this condition and received 7.52 x 10^6 / kg.

Onco-hematological patients classically presents clinical conditions and are submitted to therapies that interfere in the response to platelet transfusion. The conditions found in the 3 patients with platelet refractoriness and about the 2 patients with vascular events, they present features described in the literature, reinforcing the importance of the presence of these factors as a cause of refractoriness and vascular/endothelial involvement in patients submitted to BMT. Endothelial markers studies may help in the early identification of patients at risk of developing vascular complications, such as venocclusive disease and Engraftment Syndrome, enabling the beneficial introduction of curative and prophylactic therapies.

Conclusion:

It is possible that larger samples demonstrate other factors that influence the number of platelets transfusion events and the platelet transfusion increment of patient undergoing high doses of chemotherapy protocols and BMT. A small sampling limits comparisons and significant statistical inference, however, we cannot rule out the relevance of a descriptive analysis of the results, especially considering that each patient should be evaluated in an individualized way in clinical practice.

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Table 1 - Demographic, clinical and laboratory characteristics

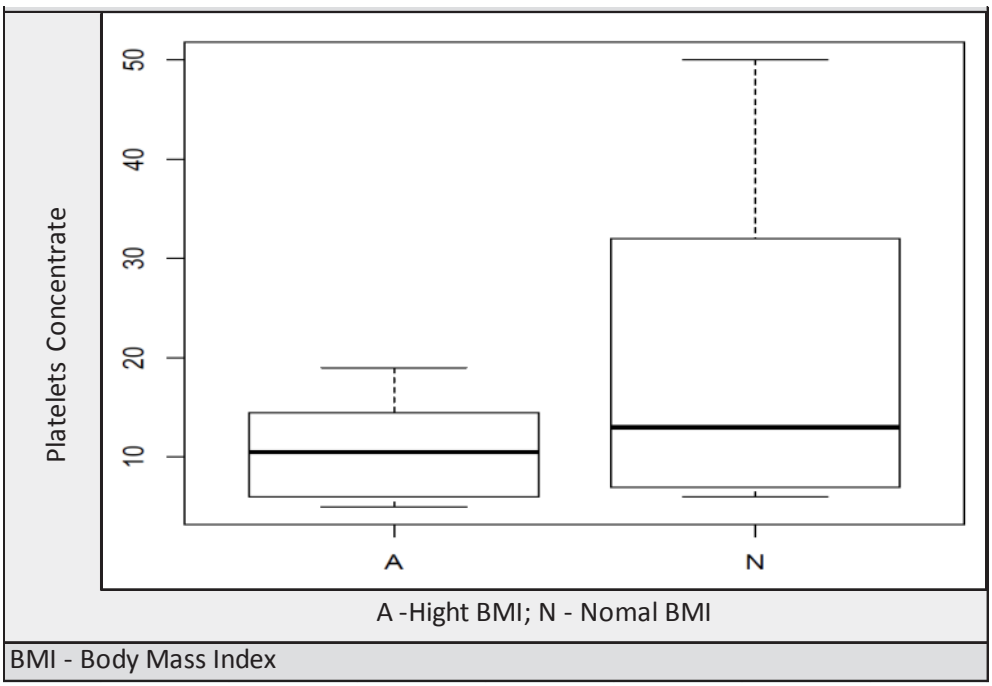
AGE	AVERAGE	39 14- 61	%
Sex	Male	13	52
	Female	12	48
Diagnostics	MM	10	40
	HL	4	36
	NHL	4	16
	AML	1	4
	CML	1	4
Radiotherapy	Yes	7	28
	No	18	72
Type of transplant	Autologous	19	76
	Allogenic	6	24
Weight (kg)	Average	76,2 Kg	
High BMI	Yes	16	64
	No	9	36
Vascular Events	Yes	2	8
	No	23	92
High Ferritin	Yes	9	36
	No	16	64
High RCP	Yes	19	76
	No	6	24
Platelet transfusion	Yes	19	76
	No	6	24
Unsatisfactory 24h ICC	Yes	3	12
	No	22	88

MM - Multiple Myeloma; LH - Hodgkin's Lymphoma; LNH - Non-Hodgkin's lymphoma; AML - Acute Myeloid Leukemia; LMC - Chronic Myeloid Leukemia; BMI - Body Mass Index; RCP - Reactive C Protein; CCI - Corrected Increment Count
Source: Prepared by the Author

Table 2 - Characteristics of patients with increased BMI

CHARACTERISTICS	BMI (KG/M2)				
	< 18,4	18,5 a 24,9	25 a 29,999	30 a 34,9	35 a 39,9
Age	38	35,8 ± 9,9	37,7 ± 10,1	38 ± 10,9	51,33 ± 15,1
Weight (kg)	46	71,3 ± 5,6	73,28 ± 12,1	90,3 ± 17,9	88,5 ± 8,4
Duration of Neutropenia	13	10,71 ± 2,1	8,9 ± 1,8	9,25 ± 0,9	7,33 ± 0,6
Days with Fever	1	5 ± 3,2	1,4 ± 1,5	4,5 ± 2,5	2,66 ± 2,1
Ferritin (ng/mL)	139	639 ± 743	301 ± 306,7	619 ± 925,3	333 ± 83,8
RCP (mg/l)	32	11,9 ± 9,8	15,14 ± 23,6	29 ± 40,3	7,5 ± 4,8
Patients with vascular events (%)	0	4	4	0	0
Patients with more than 2 events of Platelet					
Transfusion (%)	4	24	12	8	0
Patients with unsatisfactory CCI 24h (%)	0	8	4	0	0

Data given in Median ± Standard Deviation
BMI - Body Mass Index RCP - Reactive C Protein; CCI - Correct Count Increment
Source: Prepared by the Author



Graph 1 - Median of Platelets Concentrate per transfusion event

Table 3 - Patients with platelet refractoriness

CHARACTERISTICS	PATIENT 1	PATIENT 2	PATIENT 3
Age	50	33	61
Sex	Female	Male	Male
Diagnosis			
	LNH	LH	MM
Transplant	Allogenic	Allogenic	Autologous
BMI (Kg/m2)	22,3	21,6	29,1
Fever	Yes	Yes	No
Ferritin (ng/ml)	2000	1341	79
RCP (mg/l)	4	1	16
SOS	Yes	0	0
Splenomegaly	No	Yes	No
Transfusion reaction	No	No	No
Bleeding	No	No	No

LH - Hodgkin's Lymphoma; LNH - Non-Hodgkin's Lymphoma; MM - Multiple Myeloma; BMI - Body Mass Index; RCP - C Reactive Protein; SOS - Sinusoidal Obstruction Syndrome
Source: Prepared by the Author

Table 4 - Patients with vascular events

CHARACTERISTICS	VASCULAR EVENT	
	Patient1	Patient 2
	SOS	Engraftment Syndrome
Age	50	25
Sex	Female	Female
Diagnosis	LNH	LNH
Previous radiotherapy	Yes	No
Transplant	Allogenic	Autologous
Conditioning	MEL + FLU	LEAM
CD 34+ cells	3,57	7,52
Days of neutropenia	13	9
BMI (kg / m 2)	22,3	30,8
Days of fever	5	4
Ferritin(ng/mL)	2000	34
RCP (mg/l)	4	8
Platelets Transfusion Events	7	3
Unsatisfactory ICC 24 h	Yes	No

SOS - Sinusoidal Obstruction Syndrome; LNH - Non-Hodgkin's lymphoma; MEL - Melphalan; FLU - Fludarabine; LEAM - Lomostine, Etoposide, Cytarabine, Melphalan; BMI - Body Mass Index; RCP - Reactive C Protein; CCI - Corrected Increment Count.
Source: Prepared by the Author