ORIGINAL ARTICLE

Evaluation of the Inflammatory and Nutritional Status in Different Phases of Bone Marrow Transplantation

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ABSTRACT

Bone marrow transplantation in patients diagnosed with hematological cancer has high curative potential, but there is a possibility of the emergence of some adverse effects on the individual's health, such as systemic infections, which may lead to a sepsis or septic shock, which may result in the patient's death. Thus, this study aims to evaluate the inflammatory and nutritional status of patients transplanted from bone marrow in the different phases of the treatment. This research is a descriptive study with a quantitative approach and cross-sectional design, involving 14 individuals transplanted from bone marrow, with evaluation of inflammatory indicators and nutritional status. Among the 14 individuals surveyed, it was observed that there was no statistically significant difference between the phases of treatment, albumin, PCR and mPNI, however the values of neutrophils, lymphocyte, mPINI, and NRL had statistical significance with the phases of Transplant stage. The analysis of inflammatory markers in this study shows useful tools, thus it is suggested the analysis of inflammatory biomarkers as part of the clinical nutritional assessment of these individuals.

Key words: Bone Marrow Transplantation, Inflammatory state, inflammatory markers.

INTRODUCTION

The advances in medicine through diagnostic and therapeutic technologies and the intense care for cancer patients have contributed considerably to the survival of these individuals; however, statistics show that in Brazil the evolution of cancer follows a progressive scale, characterizing it as a relevant public health hazard.[1]

It is estimated for the 2018-2019 biennium that approximately 600,000 new cases of cancer will occur. Among the several types of cancer, hematological neoplasms account for about 9% of cancers in Brazil, which are characterized by changes in the blood, bone marrow, and lymphatic system? As for hematological neoplasms, it was estimated that in Brazil there are approximately 10,240 new cases of Non-Hodgkin Lymphoma (NHL). As for Hodgkin Lymphoma (HDL), it was estimated that 1,460 new cases in men and 1,010 in women. However, there are no concrete estimates regarding Multiple Myeloma.[2]

Hematopoietic Stem Cell Transplantation (HSCT), commonly known as Bone Marrow Transplantation (BMT), has been presented as a therapeutic treatment with great effectiveness in increasing the survival of transplanted patients, having a high curative potential in the approach of patients affected by hematological and non-hematological malignancies, including lymphomas, leukemias, multiple myeloma, neuroblastoma, medullary aplasia, among others.

The BMT has a few stages, namely: the conditioning phase (pre-transplant period), an episode in which the patient's organism is prepared to receive the healthy cells by BMT. During this period, the patient is submitted to high doses of chemotherapy and radiotherapy, which aim to destroy the damaged cells before the new marrow is received. Soon after the marrow

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is packaged, the process of infusing the new marrow into the individual's bloodstream (transplantation itself) occurs, a procedure similar to blood transfusion, with the installation of the infused cells in the bone marrow occurring afterwards.[3]

The post-transplant period includes the medullary aplasia period, which is characterized by a reduction in the number of blood cells (platelets, red blood cells, and leukocytes), this episode is due to the previous chemotherapy, associated with an immediate inability to reproduce enough cells. Then comes marrow recovery, known as the "marrow grip," where the continued return of blood functions occurs.[4]

However, there are numerous significant side effects in patients undergoing this type of procedure, such as: toxicity, graft-versus-host disease, bleeding, and especially acute and/or systemic infections. Such complications are capable of causing worsening in nutritional and functional status, consequently leading to clinical worsening of their general. [5]

Currently, several studies have highlighted an important association between nutritional depletion and increased levels of inflammation in patients diagnosed with cancer.[6]

It is known that these patients are in a constant inflammatory process, which can be evidenced by the alteration of some biochemical markers, which is probably caused by an attempt to attenuate the chronic inflammation. There is evidence that recurrent inflammation plays a role in the progression of cancer treatment, besides causing frequent sepsis, septic shock, and other complications that can lead to death.[7]

Knowing the importance of inflammatory control in transplanted patients and considering that there is a scarcity of scientific findings that portray this theme, the development of the present study is justified, which aims to evaluate the inflammatory and nutritional risk of bone marrow transplant patients in different phases of treatment.

METODOLOGY

Sampling Universe

This is a descriptive study with a quantitative approach and cross-sectional design, involving 14 individuals who were seen by the Bone Marrow Transplant (BMT) sector in a hospital that is a reference in the northeastern region for bone marrow transplantation, the only hospital unit in Rio Grande does Norte qualified by the Ministry of Health to perform this procedure. The sample was obtained by convenience and corresponds to all patients undergoing bone marrow transplant treatment during the research period, which occurred between May and July 2019.

This work belongs to the research line of the nucleus of study in metabolism-NEPmet, being approved by the Research Ethics Committee of the Norte Riograndense League Against Cancer, under protocol number CAAE nº 08177419.8.0000.5293, according to resolution nº 466 of December 2012.[8]

Inclusion and Exclusion Criteria

Patients over the age of 18, candidates for bone marrow transplantation, diagnosed with hematological cancer in different clinical stages, were included in the research. Patients with severe or uncontrolled mental illness, cognitive dysfunction, a history of antidepressant and/or anxiolytic use, or with a break in treatment, and/or individuals contraindicated from bone marrow transplantation were excluded from the research.

Data Collection Instruments and Techniques

All the individuals interviewed, without exception, had good communication, understanding, and consented in writing to participate in the study by signing the Informed Consent Form ICF (Appendix A), who received a copy of the document duly signed by the responsible researcher and attached to their hospital records. The researchers' copy of the ICF was archived in order to provide evidence of the research team's support for the 5-year period.

Anthropometric Evaluation

All patients had their nutritional status assessed; anthropometric variables were also recorded, including usual and current body weight, and height.

Weight and height were measured using the following instrument: Balmak® fixed electronic scale with adult ruler, with a capacity of 200 kg, and measured as follows: the scale was positioned on a flat, firm surface away from the wall and turned on before the subject was placed on it.

The subject was taken to the scales, where he/she was placed in the center of the equipment wearing light clothing and no accessories, so that there would be no intervention in the result. The subject was positioned erect, with feet together and arms extended along the body, initially checked for weight and then for height, according to Lohman.[9]

BMI - Body Mass Index

For the classification of Body Mass Index (BMI), the reference was obtained for adult individuals according to the World Health Organization - WHO (1997)[10], and for elderly individuals.

Weight loss percentage

The percentage of weight loss (%WL) was calculated according to the formula: [(usual weight - current weight) x 100/usual weight], and was classified according to Blackburn (1977), considering the period of weight loss.

Inflammatory Biomarkers and their Relationships

To evaluate the inflammatory status and prognosis of the

individuals in question, such inflammatory markers were taken into consideration: Neutrophil/Lymphocyte Ratio (NLR), Prognostic Nutritional Index (PNI), and the adapted version of the Prognostic Inflammatory and Nutritional Index (PINI).

The laboratory tests, such as C-reactive protein (CRP), albumin, neutrophils, and lymphocytes, were necessary for the classification of the aforementioned markers, which had already been previously requested by the unit's routine medical protocol (Annex A), and were performed in the same laboratory unit, based on the same reference values.

The results of the biochemical tests, in addition to access to the clinical diagnosis were captured through the printed medical records present in the unit, more specifically in the sector's nursing station. It is worth mentioning that these results were only obtained after the research participants and the responsible researcher confirmed the signature of the ICF.

Modified Nutritional Prognostic Index

The Modified Nutritional Prognostic Index (mMNPI) was calculated by the following formula: 10 × serum albumin concentration (g/dL) + 0.005 × lymphocyte counts (mm3), with the following as reference values: < 40 were related to the worst nutritional prognosis and ≥ 40 value considered within normality values.[11]

Prognostic Inflammatory and Nutritional Index

The adapted version of the Prognostic Inflammatory and Nutritional Index (PINI), determined through the CRP/albumin ratio, classifies individuals with results: <0.4 no inflammatory and nutritional risk, values between 0.4 and 1.2 as low risk, 1.2 to 2.0 moderate risk, and >2 high risk of complications.[12]

Neutrophil to Lymphocyte Ratio

For the calculation of this ratio the formula was applied: . After the result of the calculation, it was averaged and classified using the following reference: values ≥5 are considered abnormal.[7]

Mortality Frequency

As for the relative mortality frequency among the patients included in the research, the occurrence of deaths was verified through the medical records of the unit in question, and the relative frequency was calculated by simple rule of three, resulting in percentage (%) of deaths.

Statistical Analysis

All collected data was initially entered into the Excel® 2010 software database. After this procedure, the data was exported to the Prism software, version 7.0, to proceed with the statistical analysis.

The measures, in the form of continuous variables, being tested for the nature of their distribution and were presented using the measures of central tendency and dispersion (mean and standard deviation). To identify the nature of the data distribution the Kolmorov-Smirnov test was used at the 5% significance level.

A student's t-test was performed, with the objective of challenging possible differences throughout the experiment. If significant differences were detected, $P<0.05$ was used.

RESULTS AND DISCUSSIONS

The casuistic of this study consisted of sick individuals diagnosed with some type of hematological cancer, with a mean age of 48.5 ± 16.5, of which 9 were women and 5 were men.

Of the total 14 patients included in the study, 6 of them, which correspond to 43%, were diagnosed with Multiple Myeloma (MM) presenting itself as the most common hematological neoplasm in this study. Multiple myeloma is known to account for 10% of hematologic cancers worldwide, with a higher prevalence in adults and the elderly.[13] this is analogous to what was observed in the present study.

One individual was diagnosed with Non-Hodgkin Lymphoma (NHL) and another individual with Hodgkin Lymphoma (HDL), corresponding to a frequency of 7% each. Studies indicate that developed countries have a higher prevalence in young adults with an average age of 20 years, but there are statics that point to the increasing onset in adults after the age of 50.[14] these estimates are very close to what can be seen in table 1.

As for the occurrence of lymphomas, 2 individuals were diagnosed with Acute Lymphocytic Leukemia (ALL), and it is noticeable that the diagnosis of Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML) has the same percentage amount as above.

Regarding the manifestation of leukemias, statistics indicate around 30 to 40% of diagnoses occur predominantly in individuals with an average age of 18 years.[15]

Table 1. Characterization of the sample: patients in BTM in a reference hospital, Natal-RN, 2019.

Variables	Total sample (n=14)
Age (years); mean (SD)	**48.5 ± 16.5**
Age Group - n (%)	
Adult	9 (64)
Elderly	5 (36)
Gender - n (%)	

Male	5 (36)
Female	9 (64)
Type of cancer - n (%)	
NHL	1 (7)
MM	6 (43)
HDL	1 (7)
ALL	2 (14)
AML	2 (14)
CML	2 (14)
Death - n (%)	1 (7)
Current weight (kg); mean (SD)	63.. ± 16.1
BMI (kg/m²); mean (SD)	24.8 ± 4.9
BMI Classification - Adult- n (%)	
Low weight	2 (22)
Eutrophy	2 (22)
Overweight	4 (44)
Obesity Level I	1 (11)
BMI classification - Elderly - n (%)	
Low weight	2 (40)
Eutrophy	2 (40)
Overweight	1 (20)
% WL; mean (SD)	
1 week	2.33 ± 1.3
Severity of %WL - n (%)	
1 - 2% in 1 week	4 (50)
>2% in 1 week	4 (50)

Source: Author himself

N= absolute frequency; N(%)= relative frequency; NHL= Non-Hodgkin Lymphoma; MM= Multiple Myeloma; HL= Hodgkin Lymphoma; ALL= Acute Lymphocytic Leukemia; AML= Acute Myeloid Leukemia; CML= Chronic Myeloid Leukemia; BMI= Body Mass Index; %WLP= Weight Loss Percent; SD= Standard Deviation

Regarding current weight, it was found an average of 63.6 kg, with a general average Body Mass Index (BMI) (adult and elderly) of 24.8 kg/m², which is within the eutrophic classification. However, the average nutritional status classification obtained by BMI indicates overweight for most of the adult individuals (44%).

Considering that the critically ill patient has a barrier in his/her nutritional evaluation, due to changes in the distribution of body fluids (edema formation). Thus, at the moment that BMI is analyzed alone, it becomes a vague predictor measure, making it necessary to compile other data such as percentage of weight loss (%WL) and laboratory tests to perform the evaluation of the nutritional status of this individuals.[16]

However, when it comes to cancer patients, numerous gastrointestinal changes, such as: mucositis, dysphagia, diarrhea, vomiting, in addition to metabolic factors such as recurrent inflammatory process, increasing catabolic state, raising energy needs, which implies increased nitrogen excretion, corroborating significantly to involuntary weight loss of these individuals, even in patients who are overweight and obese.[17]

As seen in Table 1 the percentage of weight loss WL% in the one-week period, was 50% significant weight loss and 50% severe weight loss, which justifies the above statement. It is known that uninterrupted weight loss opportunizes the individual to infectious diseases, increased number of hospitalizations and length of hospital stay, in addition to unfavorable prognosis, consequently leading to reduced quality of life and increased mortality among this patients.[18]

Among the patients analyzed, it was found during the research period the occurrence of 01 death, caused by septic shock, which is the state of imbalance in cellular oxygen exchange, triggered by inflammation of the immune system, when there is exposure to infectious agents in the bloodstream, with high prevalence in cancer patients.[19]

In Table 2, it´s possible to see the relationship between inflammatory markers and the treatment period of transplanted patients. No statistically significant difference was found between treatment phases and albumin (p= 0.572), CRP (p=0.554) and PNI (0.674). In contrast, the markers: neutrophil (p=<0.0001), lymphocyte (p=<0.0001), the PINI (p= 0.0277), and NRL (p=<0.0001), have statistical significance to the stages of transplantation.

In this study several inflammatory markers can be seen with their altered levels. Among the inflammatory markers analyzed, it was possible to observe that the average of neutrophil and lymphocyte had a significant decrease in their values, unlike the CRP that had a significant increase, especially when compared to the values of these markers pre and post bone marrow transplantation (BMT).

Albumin remained with its values equal, with no significant difference, when compared pre- and post-transplantation, however, these values indicate hypoalbuminemia (< 3.5 g/dL), which is an episode resulting from systemic inflammation and is directly associated with a worse prognosis in cancer patients. Since albumin is a negative acute phase protein, which tends to attenuate its serum concentrations during an inflammatory process, resulting from the inhibition of its synthesis by pro-inflammatory cytokines.[7]

Table 2. Inflammatory markers and treatment periods - BMT

	BMT Pre-Treatment Mean/SD	BMT itself Mean/SD	BMT Post-Treatment Mean/SD	P
Albumin (g/dL)	3.00 ± 0.62	3.30 ± 0.61	3.00 ± 0.591	0.572
CRP (mg/L)	4.00 ± 1.65	5.00 ± 3.47	7.00± 8.10	0.554
Neutrophil (mm^3)	9039 ± 337.7	8665 ± 192	4613 ± 3999.6	<0.0001
Lymphocyte (mm^3)	2309 ± 1849.4	1833 ± 1367	504 ± 110.26	<0.0001
PINI	1.23 ± 0.15	1.16 ± 0.14	1.40 ± 0.20	0.0277
NRL	3.70 ± 0.43	3.85 ± 0.42	2.71 ± 0.32	<0.0001
mPNI	39.50 ±16.52	38.50 ± 16.42	34.14 ± 11.54	0.674

Source: Author himself

BMT=Bone Marrow Transplant; SD=Standard Deviation; CRP= C Reactive Protein; PINI= Prognostic Inflammatory Index Nutrition; NRL=Neutrophil Lymphocyte Ratio, mPNI= Modified Prognostic Index Nutrition

It was pointed out in a systematic review that often studies analyzed, 90% demonstrated a positive correlation between serum albumin and better prognosis when albumin reached its levels higher than 3.5 g/dL during cancer pre-treatment.[20]Thus, it is thought that combating hypoalbuminemia can have a positive effect on the survival of these patients.

In the case of neutrophils, these values were compared during treatment and after BMT, with a significant difference, when analyzing their numbers in each stage of treatment it is possible to observe that all the averages are within the reference values (1600 a 8000 mm^3), but as already mentioned, there was a marked decrease in relation to pre- and post-transplantation. The sharp drop in neutrophils generates a decrease in the action of body barriers (mucous membranes), in addition to changes in the microbiota, which predisposes to a high potential for infection.[21]

Regarding lymphocytes, it is observed that there was a drastic reduction in their numbers and in relation to their average in the post-BMT period, where the p-value connotes a significant difference (p= <0.0001). Analyzing the average obtained after BMT, it can be said that there is a possible picture of lymphopenia (lymphocytes < 800 mm^3) among these patients studied.

It is known that a significant decrease in lymphocytes is associated with increased morbidity and mortality, and when related to weight loss, it has an unfavorable impact on the production of immune system defense cells, leading to immunological impairment of the patient, which can increase the frequency of infections, corroborating the worsening of the disease.[22]

Unlike the values of neutrophils and lymphocytes, when we observed the evolution of their levels in relation to the treatment phase and did not observe significant difference, it can be seen that the CRP obtained a considerable increase in their values, being very close to the upper limit of normality (up to 8.0 mg/L), it is understood that the C-reactive protein is considered an important marker of inflammatory status, being one of the most used variables in the analysis of inflammatory response, which may be possible to monitor the success of treatment and detect easily possible infections.[21]

In contrast, there are limitations to patient evaluation based on CRP values due to its half-life estimated at 19 hours; since its concentration can be low, or considerably normal at the beginning of the inflammatory process first 12 hours.[23]

In the present study, when the neutrophil/lymphocyte ratio (NLR) was compared to its average values before and after BMT, it can be observed that there was a gradual decrease in its levels, with a significant association in relation to the stages of transplantation. It can be seen that these values are below the reference value (<5 value considered adequate, ≥5 were considered abnormal), in which case it is considered a significant result for these individuals, especially in the pre-transplantation phase.

Among several biomarkers used in hospital clinical practice, NLR has been suggested as a predictor of prognosis in surgical procedures, as a representative parameter of the patient's inflammatory state, and has been reported in several studies as an independent and valuable prognostic factor for different neoplasms.[24]Other studies indicate that neutrophil/lymphocyte ratio when elevated pre-treatment may be associated with poor prognosis as well as disease progression and even metastasis.[25]

The adapted version of the Prognostic Inflammatory Nutritional Index (PINI), determined by the CRP/albumin ratio that lies between the values 1.16 to 1.40, have low risk and moderate risk classification, respectively, obtaining significance in relation to the treatment phases. Given that PINI can be employed in the association between nutritional status and inflammatory response.[6]

The Prognostic Nutritional Index (PNI) has a reference value = <40 for worse nutritional prognosis and > 40 value considered to be within normality. This study found values below the reference values, ranging from 34.14 to 39.50, showing a worse nutritional prognosis for these patients, with p-value = 0.674, demonstrating that there is no significant difference when compared to the treatment period (pre, during and post BMT).

In a study conducted with 41 cancer patients, it showed a similar result regarding the mPNI p-value, as even below the reference values, there was no significant difference in the treatment phases.[26]

CONCLUSION

The compilation and analysis of inflammatory markers in this study show to be useful tools, being possible to evaluate the inflammatory and nutritional risk of transplanted patients, since a large part of the markers in altered conditions is linked to the worsening of the patient's condition during the evolution of the transplant, besides being a quick and easy-to-interpret tool, capable of providing assistance in clinical therapy, visualizing in a more effective way possible complications resulting from the treatment.

In view of such evidence related to the inflammatory and nutritional status in the phases of bone marrow transplantation, we suggest the need for measurement and analysis of inflammatory biomarkers, as an important part of the clinical and nutritional evaluation of these individuals, considering that the present study is promising in this field, more studies are needed in this area for better prognostic accuracy.

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