

## PSYCHOLOGICAL SUFFERING OF PATIENTS TRANSPLANTED WITH HEMATOPOIETIC STEM CELLS

### *SOFRIMENTO PSICOLÓGICO DE PACIENTES TRANSPLANTADOS COM CÉLULAS-TRONCO HEMATOPOÉTICAS*

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**ABSTRACT:** Hematopoietic stem cell transplantation (HSCT) affects serious risks for the patient, including death. For this reason, it is considered a treatment that can cure or can present morbidities and lead to death. In this context, patients experience the first psychological conflicts before this transplant. To describe the psychological suffering developed by patients transplanted with hematopoietic stem cells from a referral service in the state of Rio Grande do Norte. This is a cross-sectional study with a quantitative, descriptive, hospital-based approach developed with patients submitted to HSCT at a referral service in the state of Rio Grande do Norte. Data were collected between March and September of 2016, through the evaluation of the medical records of 43 patients who underwent HSCT and developed some type of psychological distress. Among 43 patients with psychological disorders, 51.16% were female, 62.79% developed anxiety 32.56% developed insomnia and 20.93% developed depression. Of these, 27.91% had a main diagnosis indicating the transplantation of Multiple Myeloma (MM), and 58.14 received autologous transplantation. It was observed that the patient had psychological suffering from the diagnosis until the end. The health professional praxis also must go beyond the resolution of physical human responses and, especially in these cases, it should aim at the early identification of signs and symptoms of psychological distress, being possible to achieve the real health needs and treat them with effectiveness.

**KEYWORDS:** Depression. Anxiety. Sleep initiation and maintenance disorders. Quality of life. Hematopoietic stem cell transplantation.

### INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has significantly modified the prognosis of patients with hereditary or acquired hematological, oncological and immunological diseases and it is the last effective alternative when conventional therapies do not provide good prognosis (FERMO et al., 2016; AZEVEDO et al., 2017). This procedure consists of painless intravenous infusion of healthy hematopoietic stem cells (HSC) extracted from bone marrow (BM), peripheral blood (PB) and placental and umbilical cord blood (PUCB), capable of restoring spinal cord function and immunology of patients with indication for transplantation, with the possibility of cure or increase in disease-free

survival (HENIG; ZUCKERMAN et al., 2014; AZEVEDO et al., 2018).

HSCT is an efficient form of treatment when the pathological process involves BM or when hematopoietic toxicity is the limiting factor in the aggressive treatment of the disease. (BAKHURAYSAH; SIATSKAS; PETRATOS, 2016). The high doses of chemotherapy used in HSCT make it an aggressive process, causing toxicity and can generate significant complications and several side effects adding feelings of worry, anguish, anxiety, among others (KUBA et al., 2017), associated with the results of the procedure and require a process of hospitalization and prolonged hospital recovery.

Also, drastic changes in daily living habits, changes in body image, long duration of treatment, periods of hospitalization and protective isolation, feeling of loss of control, fear of death and lack of information about the disease or course of the disease treatment also generate psychological distress in these patients that can occur at any stage of HSCT (ANNIBALI et al., 2017).

When there is an indication for HSCT due to the failure of other treatments, the patient and his/her relatives experience highly stressful situations and the impact of the new reality can trigger experiences of losses and uncertainties regarding the future, a fact that significantly interferes with the quality of life of patients and family members. It is perceived that the feeling of safety that follows the healthy person is quickly abolished (OGUZ; AKIN; DURNA, 2014).

In the conditioning phase and in the immediate and late post-transplant period, the patient experiences the greatest number of physical, emotional/psychological and social changes resulting from the therapeutic itinerary, changes in individual roles and social isolation. The post-transplantation time around 100 days represents a reference in the trajectory of the treatment since it is a stage in which a large part of the complications with lethal potential occur, such as Graft versus Host Disease (GVHD) (PROENÇA et al., 2016). Patients who experience complications for long periods are more susceptible to the development of psychological disorders (KAPUCU; KARACAN, 2014).

For this study, psychic suffering is characterized as any psychological/mental change developed by patients during hospitalization and duly recorded in patients' medical records and the outcome refers to the procedure of HSCT. In view of the above, this study aimed to describe the psychological suffering developed by patients transplanted with hematopoietic stem cells from a referral service in the state of Rio Grande do Norte, Brazil.

## MATERIAL AND METHODS

This is a cross-sectional study, based on a retrospective cohort study, performed with patients undergoing HSCT at a referral service in the state of Rio Grande do Norte, Brazil.

The study was developed in a reference hospital for high complexity care, located in the capital of the state of Rio Grande do Norte, Brazil. The choice of this health service was due to be the only one of the state authorized, accredited,

qualified and responsible for the implementation of HSCT since 2004, agreed to the Brazilian Unified Health System, which meets the needs of the patients with an indication for transplantation.

All medical records of patients submitted to HSCT were searched in the health service surveyed. The final sample consisted of 272 HSCT performed in the whole period, of which 43 patients who developed one or more types of psychological distress during the hospital stay, in the pre, intra-transplant or post-transplant phases. The data were collected between March and September 2016, through the records of registered patients who performed HSCT in the service from February 2008 to December 2015. That is eight years of procedure. The data were collected from the Medical Archive and Statistics Service.

The data were collected by a student of the master's degree course and three scientific initiation fellows properly trained for the objectives of the research, approaching the topic by expositive-discussed class and reading texts and clarification of the constant variables in the research instrument.

The following clinical and epidemiological characteristics of cases were analyzed: gender, age, race marital status, hematologic disease, type of HSCT performed and psychological disorders developed. The psychological disorders were found in psychologist and nurse assistance shown in the medical records. The statistical free software R, version 3.0.0 was used for the descriptive analysis of the data. For the description of the sample, a table containing absolute and relative frequencies was used.

The Protocol for this Research was submitted to the Research Ethics Committee of the Federal University of Rio Grande do Norte, in accordance with Resolution 466/12 of the National Health Council of the Ministry of Health under the opinion 1,132,720. The research authorization was requested from the institution where the research was carried out by a Letter of Consent and a Term of Concession. All the fundamental principles of bioethics inherent to autonomy, beneficence, non-maleficence, and justice were obeyed.

## RESULTS AND DISCUSSION

Forty-three out of the 272 patients who underwent HSCT in the study period presented one or more types of psychological distress. The age ranged from 14 to 67 years old with a mean age of 42.07 years old and 51.16% of them were female. Among the patients who underwent HSCT and presented psychological disorders, 27.91% had as

the main diagnosis that indicated the transplantation of Multiple Myeloma (MM), 58.14 received autologous transplantation and the most cited

psychological suffering in the medical records was anxiety (62.79%) (Table 1).

**Table 1.** Sociodemographic and clinical characteristics of patients submitted to HSCT from 2008 to 2015: Natal /Rio Grande do Norte, Brazil, 2016 (n = 43).

VARIABLES	n	%
<b>Gender</b>		
Female	22	51.16
Male	21	48.84
<b>Age Group</b>		
Up to 30 years old	11	25.58
31 – 60 years old	28	65.12
More than 60 years old	4	9.30
<b>Race</b>		
Brown	15	34.88
White	10	23.26
Black	1	2.33
Missing	17	39.53
<b>Marital status</b>		
Married	22	51.16
Single	15	34.88
Others	4	9.30
Missing	2	4.65
<b>Hematologic disease</b>		
Multiple myeloma	12	27.91
Acute myeloid leukemia	8	18.60
Acute lymphoblastic leukemia	8	18.60
Non-Hodgkin's lymphoma	7	16.29
Others	8	18.60
<b>Type of HSCT performed</b>		
Autologous	25	58.14
Allogenic	18	41.86
<b>Psychological disorders developed *</b>		
Anxiety	27	62.79
Depression	9	20.93
Others	9	20.93
<b>Total</b>	<b>43</b>	<b>100.00</b>

Note: \*Multiple answers.

Initially, the sample was characterized by gender and age and the results approximate the data found in a study conducted in Iran, in which 47% of the patients were female (VAEZI et al., 2016). MM was the most prevalent hematologic disease diagnosis among patients in this study and corroborates the number of autologous transplantations that were also performed in patients with non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD) and others (AZEVEDO et al., 2018).

Autologous transplantation is indicated mainly for MM, NHL, HD, neuroblastoma, germ cell tumors, autoimmune diseases, amyloidosis and others. And allogeneic HSCT is indicated for Acute Myeloid Leukemia, Acute Lymphoblastic

Leukemia, Chronic Myeloid Leukemia, Myelodysplastic Syndromes, Aplastic Anemia, Fanconi Anemia, Sickle Cell Anemia, among others (PERUMBETI; SACHER, 2016; FABRICIUS, RAMANATHAN, 2016).

The psychological disorders highlighted in Table 1 were identified shortly after hospital admission, a few days before the infusion of HSC and in the first 15 days after transplantation. According to the data presented, it was possible to notice that the number of patients who presented anxiety disorder was exactly triple when compared to the depression.

In a study carried out in Turkey on the quality of life of patients before and after HSCT,

anxiety, depression, decreased physical and mental quality of life were reported IN transplant patients who stated that the disease requires treatment and hospitalization for long periods, changes in the quality of life body image and concern for the future (OVAYOLU et al., 2013).

Hospitalization is considered to be a disruptive and life-altering situation since it includes a number of factors such as declining health status and separation from the family and social context. Besides causing changes in the routine of the patient and the whole family, it can trigger changes, such as anxiety (GOMES et al., 2016).

Psychological suffering such as depression, anxiety, and sleep disorders may lead to a reduction in the quality of life of transplanted individuals, when added to the physical aspects (pain, chemotherapy-related toxicity, nausea, vomiting, among others) and social aspects (social isolation related to prolonged hospitalization period) (PROENÇA et al., 2016).

These patients are physically and psychically fragile after a long period between diagnosis, initiation of the treatment and indication for HSCT. Thus, their anxiety levels are very high, both regarding transplantation and the hope of cure or disease remission, situation that causes an intense suffering (PEREIRA; CORTEZ, 2014).

Anxiety is indicated as a reaction of the individual to a real danger or threat to their physical or biological integrity and their symptoms appear unexpectedly, that is, they may occur before or immediately upon exposure to a situation causing anxiety. However, anxiety is considered an adaptive phenomenon necessary to cope with everyday situations characterized by physical manifestations such as tachycardia, hyperventilation, sweating, muscular tension, increased blood pressure, as well as behavioral and emotional symptoms, such as fear, apprehension, and agitation (SANTIAGO; HOLANDA, 2013). In the case of transplant patients, it is mainly related to the current state of health and hospitalization.

The diagnosis of depression is complex, especially when the individuals are hospitalized since several environmental factors and the physical health state can interfere in the diagnosis. The most recurrent signs and symptoms of depression are the ability change to experience pleasure, loss of interest, decreased the ability to concentrate, fatigue, drowsiness or insomnia, and decreased appetite. Also, decreased self-esteem, self-confidence, and guilty and unworthiness are common. The number and severity of such symptoms determine the levels

of depression in mild, moderate and severe (GOMES; NÓBREGA, 2015).

A study carried out in a hospital in the state of São Paulo, Brazil, with 13 patients submitted to HSCT, showed that nine of them presented anxiety and depression. It was also possible to note that anxiety pictures were more common than those of depression. Still, in this study, ten of the patients had stress, and five of them were in the exhaustion phase (CROVADOR et al., 2013).

In this study, 32.56% of the patients reported episodes of insomnia during hospitalization. Insomnia is considered a difficulty to start sleeping, multiple nocturnal awakenings with difficulty to return to sleep, early awakening, besides to drowsiness and persistent fatigue during the day, highlighted as one of the most common sleep disorders among hospitalized patients. Also, restlessness was identified as one of the causes of sleep interruption during hospitalization of patients with an indication for HSCT (JIM et al., 2014). In a study carried out to investigate sleep quality in 570 patients submitted to HSCT, the prevalence of sleep disorders was 45.08% before their admission and 22.10% after their discharge (JIM et al., 2018).

According to research conducted in the United States of America, 50% of the patients presented episodes of hallucination and delirium disorders, related to higher doses of opioids in the post-transplant period, considered the only risk factor for their occurrence (FANN et al., 2011).

The performance of the research in only one transplant center was a limitation for this study, which did not allow the comparison between patients from another state or region. In view of this discussion, it is worth emphasizing the importance to develop further studies related to the psychological disorders experienced by patients submitted to HSCT, which result in the presentation of evidence that provides health professionals with pertinent information for decision making, with the objective of qualifying care for these patients and their families.

## CONCLUSIONS

The psychological disorders accompany the patients from diagnosis to their outcome, causing an imbalance in their quality of life. With this, it is necessary that health professionals seek together strategies to have a direct work with these patients throughout the treatment, so they will not suffer more as a consequence of such disorders.

Under its complexity and uncertainty and while other treatments fail, HSCT is extremely

anxiogenic both for the patients and their families, as well as for the professionals who care for this specific patients. There is a gap in scientific production regarding the impact of the psychological stressors of this treatment on the patients and their relatives, opening the opportunity for further research on the theme.

This study highlights the relevance of the psychological distress diagnosis among patients submitted to HSCT significantly interfering with their recovery. Also, the praxis of the health professional must go beyond the resolution of physical human responses and, especially in these cases, it should aim at the early identification of signs and symptoms of psychological distress, being

possible to achieve the real health needs and treat them with effectiveness.

### CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article. The submitting authors are responsible for co-authors declaring their interests.

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**RESUMO:** O Transplante de Células-Tronco Hematopoéticas (TCTH) acarreta sérios riscos para o paciente, inclusive o de morte. Por esse motivo é considerado um tratamento que pode curar ou que pode apresentar morbidades e levar ao óbito. Diante desse contexto, os pacientes vivenciam os primeiros conflitos psicológicos que antecedem o transplante em si. Descrever o sofrimento psicológico desenvolvido por pacientes transplantados com células-tronco hematopoéticas de um serviço de referência do estado do Rio Grande do Norte. Trata de um estudo do tipo transversal, com abordagem quantitativa, descritiva, de base hospitalar, desenvolvida com pacientes submetidos ao TCTH em um serviço de referência do estado do Rio Grande do Norte. Os dados foram coletados entre os meses de março e setembro de 2016, mediante avaliação dos prontuários de 43 pacientes que realizaram o TCTH e desenvolveram algum tipo de sofrimento psicológico. Dentre os 43 pacientes que apresentaram distúrbios psicológicos, 51,16% eram do sexo feminino, 62,79% desenvolveram ansiedade, 32,56% insônia e 20,93% depressão. Destes, 27,91% tinham como diagnóstico principal que indicou o transplante o Mieloma Múltiplo (MM), 58,14 receberam transplante autólogo. Observou-se que o sofrimento psicológico acompanhou o paciente desde o diagnóstico até o desfecho. Ademais, a práxis do profissional de saúde deve ir para além da resolução de respostas humanas físicas e, especialmente para estes casos, deve visar a identificação precoce dos sinais e sintomas de sofrimento psicológico para que seja possível alcançar as reais necessidades de saúde e tratá-las com efetividade.

**PALAVRAS-CHAVE:** Depressão. Ansiedade. Distúrbios do Início e da Manutenção do Sono. Qualidade de vida. Transplante de Células-Tronco Hematopoéticas.

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### REFERENCES

- ANNIBALI, O.; PENSIERI, C.; TOMARCHIO, V.; BIAGIOLI, V.; PENNACCHINI, M.; TENDAS, A.; TAMBONE, V.; TIRINDELLI, M. C. Protective isolation for patients with haematological malignancies: a pilot study investigating patients' distress and use of time. *Int J Hematol Oncol Stem Cell Res.* v. 11, n. 4, p. 313-8, 2017.
- AZEVEDO, I. C.; CASSIANO, A. N.; CARVALHO, J. B. L.; FERREIRA JÚNIOR, M. A. Nursing care for hematopoietic stem cell transplant recipients and their families. *Rev Rene.* v. 18, n. 4, p. 559-66, 2017. <https://doi.org/10.15253/2175-6783.2017000400019>
- AZEVEDO, I. C.; FERREIRA JÚNIOR, M. A.; AQUINO, L. A. P.; OLIVEIRA, A. A.; CRUZ, G. K. P.; CARDOSO, A. I. Q.; IVO, M. L.; SANTOS, V. E. P. Epidemiologic profile of patients transplanted with hematopoietic stem cells in a reference service in the State of Rio Grande do Norte, Brazil. *Transplant Proc.* v. 50, n. 3, p. 819-23, 2018. <https://doi.org/10.1016/j.transproceed.2018.02.015>

BAKHURAYSAH, M. M.; SIATSKAS, C.; PETRATOS, S. Hematopoietic stem cell transplantation for multiple sclerosis: is it a clinical reality? **Stem Cell Res Ther.** v. 7, n. 12, 2016.

<https://doi.org/10.1186/s13287-015-0272-1>

CROVADOR, L. F.; OLIVEIRA-CARDOSO, É. C.; MASTOPIETRO, A. P.; SANTOS, M. A. Health related quality of life of patients with multiple sclerosis before hematopoietic stem cells transplantation. **Psicol. Reflex. Crit.** v. 26, n. 1, p. 58-66, 2013. <https://doi.org/10.1590/S0102-79722013000100007>

FABRICIUS, W. A.; RAMANATHAN, M. Review on haploidentical hematopoietic cell transplantation in patients with hematologic malignancies. **Adv Hematol.** v. 2016, p. 1-8, 2016.

<https://doi.org/10.1155/2016/5726132>

FANN, J. R.; HUBBARD, R. A.; ALFANO, C. M, et al. Pre and Post-Transplantation Risk Factors for Delirium Onset and Severity in Patients Undergoing Hematopoietic Stem-Cell Transplantation. **J Clin Oncol.** v. 29, n. 7, p. 895-901, 2011. <https://doi.org/10.1200/JCO.2010.28.4521>

FERMO, V. C.; RADÜNZ, V.; ROSA, L. M.; MARINHO, M. M. Professional attitudes toward patient safety culture in a bone marrow transplant unit. **Rev Gaúcha Enferm.** v. 37, n. 1, p. 1-9, 2016.

<https://doi.org/10.1590/1983-1447.2016.01.55716>

GOMES, G. L. L.; NÓBREGA, M. M. L. Anxiety in children following hospitalization: a proposal for a nursing diagnosis. **Rev. Latino-Am. Enfermagem.** v. 23, n. 5, p. 963-70, 2015. <https://doi.org/10.1590/0104-1169.0372.2637>

GOMES, G. L. L.; FERNANDES, M. G. M.; NÓBREGA, M. M. L. Hospitalization anxiety in children: conceptual analysis. **Rev Bras Enferm.** v. 69, n. 5, p. 940-5, 2016. <https://doi.org/10.1590/0034-7167-2015-0116>

HENIG, I.; ZUCKERMAN, T. Hematopoietic Stem Cell Transplantation-50 Years of Evolution and Future Perspectives. **Rambam Maimonides Med J.** v. 5, n. 4, p. 1-15, 2014. <https://doi.org/10.5041/RMMJ.10162>

JIM, H. S. L.; EVANS, B.; JEONG, J. M.; GONZALEZ, B. D.; JOHNSTON, L.; NELSON, A. M.; KESLER, S.; PHILLIPS, K. M.; BARATA, A.; PIDALA, J.; PALESH, O. Sleep disruption in hematopoietic cell transplant recipients: prevalence, severity, and clinical management. **Biol Blood Marrow Transplant.** v. 20, n. 10, p. 1465-84, 2014. <https://doi.org/10.1016/j.bbmt.2014.04.010>

JIM, H. S. L.; SUTTON, S.; MAJHAIL, N.; WOOD, W. A.; JACOBSEN, P. B.; WINGARD, J. R.; WU, J.; CAVALEIRO, J. M.; SYRJALA, K. L.; LEE, S. J. Severity, Course, and predictors of sleep disruption following hematopoietic cell transplantation: a secondary data analysis from the BMT CTN 0902 Trial. **Bone Marrow Transplant.** v. 53, n. 8, p. 1038-43, 2018. <https://doi.org/10.1038/s41409-018-0138-0>

KAPUCU, S.; KARACAN, Y. Physiological problems in patients undergoing autologous and allogeneic hematopoietic stem cell transplantation. **Asia Pac J Oncol Nurs.** v. 1, n. 1, p. 50-4, 2014.

<https://doi.org/10.4103/2347-5625.135821>

KUBA, K.; ESSER, P.; MEHNERT, A.; JOHANSEN, C.; SCHWINN, A.; SCHIRMER, L.; SCHULZ-KINDERMANN, F.; KRUSE, M.; KOCH, U.; ZANDER, A.; KRÖGER, N.; GÖTZE, H.; SCHERWATH, A. Depression and anxiety following hematopoietic stem cell transplantation: a prospective population-based study in Germany. **Bone Marrow Transplant.** v. 52, n. 12, p. 1651-7, 2017.

<https://doi.org/10.1038/bmt.2017.190>

OGUZ, G.; AKIN, S.; DURNA, Z. Symptoms after hospital discharge following hematopoietic stem cell transplantation. **Indian J Palliat Care.** v. 20, n. 1, p. 41-9, 2014. <https://doi.org/10.4103/0973-1075.125558>

OVAYOLU, O.; OVAYOLU, N.; KAPLAN, E.; PEHLIVAN, M.; KARADAG, G. Symptoms and Quality of Life: Before and after stem cell transplantation in câncer. **Pak J Med Sci**. v. 29, n. 3, p. 803-8, 2013. <https://doi.org/10.12669/pjms.293.3290>

PEREIRA, D. R.; CORTEZ, E. A. Emotional distress on the interdisciplinary health team of hematopoietic stem cells transplantation - an integrative review. **Medicina (Ribeirão Preto)**. v. 47, n. 2, p. 104-111, 2014. <https://doi.org/10.11606/issn.2176-7262.v47i2p104-111>

PERUMBETI, A.; SACHER, R. A. **Hematopoietic Stem Cell Transplantation**. California (USA): Medscape; 2016.

PROENÇA, S. F. F. S.; MACHADO, C. M.; COELHO, R. C. F. P.; SARQUIS, L. M.; GUIMARÃES, P. R.; KALINKE, L. P. Quality of life of patients with graft-versus-host disease (GvHD) post-hematopoietic stem cell transplantation. **Rev Esc Enferm USP**. v. 50, n. 6, p. 953-60, 2016. <https://doi.org/10.1590/s0080-623420160000700011>

SANTIAGO, A.; HOLANDA, A. F. Phenomenology of depression: a review of brazilian academic production. **Rev. abordagem gestalt**. v. 19, n. 1, p. 38-50, 2013. <https://doi.org/10.18065/RAG.2013v19n1.5>

VAEZI, M.; GHARIB, C.; SOURI, M.; GHAVAMZADEH, A. Late Complications in acute Leukemia patients following HSCT: a single center experience. **Int J Hematol Oncol Stem Cell Res**. v. 10, n. 1, p. 1-6, 2016.