JOURNAL OF SCHOOL OF NURSING USP
REVISTA DA ESCOLA DE ENFERMAGEM DA USP

ORIGINAL ARTICLE

DOI: http://dx.doi.org/10.1590/S0080-623420160000700011

Quality of life of patients with graft-versus-host disease (GvHD) post-hematopoietic stem cell transplantation*

Qualidade de vida de pacientes pós-transplante de células-tronco hematopoéticas com doença do enxerto-hospedeiro

Calidad de vida de pacientes post trasplante de células madre hematopoyéticas con enfermedad del injerto contra huésped

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How to cite this article:
Proença SFFS, Machado CM, Coelho RCFP, Sarquis LMM, Guimarães PRB, Kalinke LP. Quality of life of patients with graft-versus-host disease (GvHD) post-hematopoietic stem cell transplantation. Rev Esc Enferm USP. 2016;50(16):951-958. DOI: http://dx.doi.org/10.1590/S0080-623420160000700011

*Extracted from the dissertation "Qualidade de vida nos 100 dias do transplante de células-tronco hematopoéticas", Universidade Federal do Paraná, 2015.

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ABSTRACT

Objective: Assessing the quality of life of adult patients with hematological cancer in the 100 days after transplantation of hematopoietic stem cells and verifying whether the variable graft-versus-host disease (GvHD) is predictive of worse results. **Method:** An observational correlational and quantitative study with 36 adult participants diagnosed with hematologic cancer who underwent hematopoietic stem cell transplantation from September 2013 to June 2015. **Result:** The mean age was 37 years, 52.78% were female, and 61.11% were diagnosed with leukemia. Quality of life scores showed a significant impact between pre-transplantation and pre-hospital discharge, and also within the 100 days post-transplantation. The statistical analysis between the scores for the groups with and without GvHD showed a significant difference between the presence of the complication and worse results. **Conclusion:** Quality of life is altered as a result of hematopoietic stem cells transplantation, especially in patients who have graft-versus-host disease.

DESCRIPTORS

Quality of Life; Hematopoietic Stem Cell Transplantation; Graft vs Host Disease; Oncology Nursing.

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Received: 03/18/2016
Approved: 11/07/2016

INTRODUCTION

The number of hematopoietic stem cell transplantations (HSCT) has progressively increased in recent years and has benefited patients with hematologic cancer[1]. In Brazil 1,239 transplants were performed in 2004, and this number rose to 2,013 in 2014, with 371 of these being performed in the southern region of the country[2]. However, this therapy introduces complications, such as graft-versus-host disease (GvHD), which impacts on quality of life (QoL), in addition to interfering in biological, psychological, cognitive and social aspects of the patient and their family. Thus, it is important that health professionals assess the QoL of patients in order to help them understand and overcome what occurs during and after the transplant[3-4].

Occurrences during HSCT vary with the stages; these are didactically divided in order to consider the risks to which patients are exposed, in addition to the symptoms. Conditioning is the period immediately preceding the HSCT, characterized by infusing high doses of cytotoxic agents with the goal to eradicate the disease, inducing immune suppression in order to reduce graft rejection, which is mediated by host cells[5].

Immediate and late post-transplantation is the period in which nurses have to deal with the greatest physical, emotional and social changes arising from the therapeutic itinerary, changes in individual roles and social isolation. A post-transplantation period lasting around 100 days represents a milestone in the treatment trajectory, since it corresponds to the end of a critical period and a stage when most of the potentially lethal complications occur.

Among the complications that concern the patient after HSCT, consequences of the toxic effects of high-dose chemotherapy may be highlighted such as mucositis, diarrhea and vomiting, as well as those relating to the pre-existing comorbidities. Successful treatment of these complications is influenced by characteristics of each patient and the number of previous transfusions and susceptibility to infections caused by the post-conditioning pancytopenia period[6].

The nursing staff has an important role in inserting practices for prevention, early detection and managing the complications that follow HSCT[7], and among these is GvHD.

GvHD occurs when donor lymphocytes recognize the host as strange and initiate an immune process of attacking recipient cells[8]. It is related to epithelial tissue damage frequently caused by the conditioning regime, which leads to secreting inflammatory cytokines and culminating in the infiltration of effector donor cells attacking recipient cells[9].

This complication leads to high rates of morbidity, limiting survival and causing poorer QoL, which can occur from the earliest days preceding medullar attachment until months after HSCT[10].

Diagnoses differentiate the disease in acute and chronic broad categories by a score of clinical manifestations in affected organs, and the subcategories describe disease severity and treatment indications[11].

Acute GvHD is characterized by inflammatory components[5], where skin, liver and digestive tract are the main targets. Skin manifestations appear in the form of erythema maculopapular rash, and liver impairment is evaluated by bilirubin and liver enzyme serum levels, while the severity of gastrointestinal damage is evaluated by the presence of vomiting, diarrhea volume, abdominal pain and gastrointestinal bleeding[6]. On the other hand, chronic GvHD resembles valvular diseases that present autoimmune and fibrotic characteristics. In general it can be classified according to its affective extension, being limited when it is only located in one organ or tissue, or as extensive when spanning multiple organs[5]. The simultaneous occurrence of acute GvHD and chronic GvHD results in syndrome overlap, which is associated with high mortality rates[6].

It should be noted that the concrete need for nursing care in the course of this complication is unpredictable, since individual demands should be considered[12], and to this end, knowledge about the impact of GvHD on QoL after HSCT should be punctuated in order to provide care that minimizes changes to patient's QoL. Thus, the guiding question arises: *Is GvHD related to worsening results of QoL*?

Consequently, the present research aimed to assess the QoL of adult patients with hematological cancer in 100 days of HSCT and check if the GvHD variable is predictive of worse results.

METHOD

An observational, correlational and quantitative study performed at the Bone Marrow Transplantation Service of a public hospital in the southern region of Brazil, being a reference service for this treatment modality in Latin America.

Inclusion criteria were: being over 18 years old, diagnosed with hematologic cancer and being submitted to HSCT. Patients who did not have the physical conditions to complete the questionnaires were excluded, however there was no occurrence of such exclusion. Discontinuity criteria included death of the patient or the participant not responding to the questionnaires within the proposed period.

The study sample consisted of 36 participants, corresponding to 100% of patients with hematologic cancer who underwent HSCT at the study site; among these, 32 participants were in the pre-hospital discharge period and 25 in the 100-day post-HSCT. Losses occurred due to deaths (n = 10) and loss of follow-up contact after hospital discharge (n = 1).

Data collection was performed between September 2013 and June 2015 with 36 participants who met the inclusion criteria, and one was discontinued. The sociodemographic and clinical profile was characterized by a specific questionnaire, and two questionnaires were used for QoL evaluation: the generic questionnaire *Quality of life Questionnaire Core 30* (QLQ-C30), version 3.0 in Portuguese, developed by the *European Organization Research Treatment of Cancer* (EORTC), and *Functional Assessment Cancer Therapy – Bone Marrow Transplantation* (FACT-BMT), version 4.0 in Portuguese, specific for assessment of QoL in HSCT and developed by the *Functional Assessment of Chronic Illness Therapy* (FACIT), with both validated for Brazil.

The questionnaires were applied in three significant stages of HSCT. In Pre-HSCT, before the conditioning regimen, to establish the baseline level of QoL; at pre-hospital discharge, a period considered a milestone that ends hospitalization and initiates outpatient follow-up; and at 100 days post-HSCT, which represents the end of the critical transplant period.

Sociodemographic and clinical data were analyzed with descriptive statistics expressed in simple and absolute frequency. In relation to the data obtained from the QoL questionnaires, these were organized into tables, expressed as mean, minimum value, maximum value and standard deviation, and examined according to EORTC[13] and FACIT guidelines[14].

The non-parametric Friedman test complemented by the least significant difference test for multiple comparisons (*p-value*) were used for comparing the scores obtained in each stage, in which results with $p<0.05$ are significant. The use of non-parametric tests is justified due to the lack of normality of the data, an assumption verified by the Shapiro-Wilk Test. The pre-transplantation stage was compared with pre-hospital discharge, and the pre-transplant with 100 days post-HSCT; also, pre-hospital discharge with 100 days post-HSCT.

The global QoL score on the QLQ-C30 (score of 0 to 100 points) and the general QoL score of the FACT-BMT (0 to 148 points) were considered for statistical calculations of QoL and presence of GvHD, and then Mann-Whitney U test was applied.

Ethical aspects

After registering the research in the organizations that developed the QoL evaluation tools (EORTC and FACIT), the use of the questionnaires was authorized by download directly to the researcher in charge. Studies using instruments from these organizations are highlighted in the discussion.

This study is part of the thematic project *Evaluation of Quality of life of Adult Patients with Hematologic Neoplasia Submitted to Hematopoietic Stem Cell Transplantation*, which followed the ethical precepts of Resolution 466/12 and was developed after the approval of the Research Ethics Committee of the Biological Sciences and Health Sector of the Universidade Federal do Paraná, under opinion number 411.548/2013.

In order to insert the participants in the study, they were informed about the research objectives, voluntary participation, risks and benefits, as well as about data collection periodicity. Participants signed and received one of a two-way Free and Informed Consent Form.

RESULTS

The study population (Table 1) consisted of 52.78% (n = 19) female, with a mean age of 37 years, and 50% (n = 18) in the age group between 18 and 30 years. Regarding clinical characteristics, 61.11% (n = 22) had a diagnosis of leukemia, 41.67% (n = 15) underwent allogeneic HSCT from family donors, and 22.22% (n = 8) developed GvHD within the 100 days.

Table 1 – Characterization of sociodemographic and clinical profile – Curitiba, PR, Brazil, 2013-2015.

Variable	Absolute frequency (n = 36)	Relative frequency (%)
Age		
18-30 years	18	50
31-40 years	4	11.11
41-50 years	5	13.89
Over 50 years	9	25
Mean age	37 years	
Gender		
Female	19	52.78
Male	17	47.22
Marital status		
Married	15	41.67
Divorced	1	2.78
Single	15	41.67
Consensual union	5	13.88
Number of children		
None	15	41.67
1 child	5	13.89
2 children	9	25
3 children	4	11.11
More than 3 children	3	8.33

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Variable	Absolute frequency (n = 36)	Relative frequency (%)
Education level		
Primary education	9	25
Secondary education	17	47.22
Superior education	10	27.78
Occupation		
Economically active	21	58.33
Retired	4	11.11
Stay-at-home Mom/Wife	5	13.89
Student	6	16.67
Family income		
Up to 1 minimum wage	5	13.89
1 to 3 minimum wages	19	52.78
4 to 10 minimum wages	9	25
10 to 20 minimum wages	3	8.33
Diagnosis		
Hodgkin's Lymphoma	5	13.89
Non-Hodgkin's lymphoma	1	2.78
Acute lymphoblastic leukemia	9	25
Acute myeloblastic leukemia	10	27.78
Chronic mileloide leukemia	3	8.33
Multiple myeloma	7	19.44
Myelodysplastic syndrome	1	2.78
Time since diagnosis		
Less than 1 year	10	27.78
From 1 to 3 years	16	44.44
More than 3 years	10	27.78
Graft type		
Autologous	11	30.56
Allogeneic from family donors	15	41.67
Allogeneic from unrelated donors	10	27.77
Cell Source		
Bone marrow	15	41.67
Peripheral blood	21	58.33
GvHD within the 100 days post-HSCT		
Yes	8	22.22
No	28	77.78

QoL scores evidenced that the lowest mean is related to the pre-hospital discharge period, being 67.71 in the QLQ-C30 and 98.60 in FACT-BMT, as shown in Table 2.

Global QoL of the QLQ-C30 *p-value* did not show any significance between the stages; on the other hand, the General QoL of the FACT-BMT *p-value* shows significance between the first and second stages, and between the second and third stages (Table 3).

Table 2 – QoL scores obtained in the three stages of the study – Curitiba, PR, Brazil, 2013-2015.

Domains	Basal (n = 36)				Pre-hospital discharge (n = 32)				100 days post-HSCT (n = 25)			
	Mean	Min	Max	SD	Mean	Min	Max	SD	Mean	Min	Max	SD
Global QoL (QLQ-C30)	78.01	33.33	100	18.49	67.71	16.67	100	20.82	73.67	8.33	100	23.78
General QoL (FACT-BMT)	111.84	48	140	21.93	98.60	62	131	14.52	102	20	148	34.03

Table 3 – P-value among the three stages of the study – Curitiba, PR, Brazil, 2013-2015.

Domains	*p-value*	1st stage versus 2nd stage	1st stage versus 3rd stage	2nd stage versus 3rd stage
Global QoL (QLQ-C30)	0.1637			
General QoL (FACT-BMT)	0.00007	$p < 0.001$		$p < 0.05$

Statistical analysis between Global QoL scores (QLQ-C30) of the groups of eight with and without GvHD (n = 28) in the three stages of the study showed that patients with this complication had statistically significant worse QoL in the pre-hospital discharge period (*p-value* 0.036) and for the 100 days (*p-value* 0.029). Analysis of the General QoL (FACT-BMT) showed no significance.

DISCUSSION

The participants of this study were in the age group corresponding to the productive and reproductive phases, being economically active with an occupation and/or consolidated professions/careers, during the phase of constituting families and with responsibilities inherent to them, of which can suffer therapeutic impacts. This data corroborates a national study carried out with 30 participants in São Paulo[15], as well as an American study conducted with 662 participants[16]. Regarding gender, the study is not compatible with the cancer estimates for the years of 2014 and 2015, when hematologic malignancies presented higher incidence in men[17].

Regarding the diagnosis, the predominance of leukemias corroborates the findings of a North American study in which 60% were leukemias[16]. It is in line with the estimate for cancer in 2015 in Brazil, in which this diagnosis presents an absolute superior frequency in comparison to other hematological malignancies[17].

The most common graft type in the present study was allogeneic (69.44%), more specifically, allogeneic from family donors, with a percentage of 41.67%. Similar data were found in a North American study in which allogeneic HSCTs accounted for 53.6%[18]. However, it differs from the HSCT characteristics performed in 2014 in Brazil, where the number of autologous HSCTs (1,275) was higher than allogeneic HSCTs (738)[2].

According to the records of the Brazilian Association of Organ Transplants[2], the State where the research was carried out had a proportionally larger number of allogeneic HSCTs in relation to autologous, being the only one (state) that performed more than ten per million of the population; this evidences the relevance of the cases treated in this service, considering that allogeneic transplants have high technical complexity in relation to autologous.

The present study demonstrates that the QoL of adult patients with hematologic cancer who undergo HSCT decreases in the pre-hospital discharge period compared to the baseline period, showing a significant improvement at 100 days post-HSCT. A similar result was evidenced in a study of 159 patients diagnosed with cancer at a HSCT unit in the United States[19], unlike what was found in a public hospital in the state of São Paulo with 12 patients submitted to HSCT. In this, QoL was preserved in the pre-hospital discharge period except for the physical aspects[20]. It should be noted that both studies used the FACT-BMT instrument, so this decline in the QoL assessment regarding physical aspects may be related to the various effects resulting from the therapy.

The involvement of physical, social and emotional aspects in post-transplantation can lead to a decrease in QoL and is related to a number of factors, including: toxic effects of chemotherapy such as nausea, vomiting, inappetence, pain, skin alterations, impaired body image/perception and sexual function, as well as changes arising from the diagnosis, social isolation and prolonged hospitalization. All these experienced changes due to illness and HSCT cause symptoms such as depression, anxiety, emotional unrest, fear and a sense of uncertainty about the future.

Similar results were found in a systematic literature review that analyzed 34 articles which applied the QLQ-C30 questionnaire to approximately 2,800 cancer patients submitted to HSCT. In this review, the mean scores found in the pre-HSCT were higher than at discharge, and six months later the scores were not close, however not higher than the initial ones[21].

The data from the present study show that at the end of the evaluated period the Basal QoL score recovers. However, this data refers to patients diagnosed with cancer, close to undergoing a risky treatment with the possibility of cure. Thus, despite returning to its initial values at 100 days, QoL may be compromised due to the diagnosis of cancer. Thus, 100 days post-HSCT is not sufficient for the cancer patient to present better QoL compared to what it was before receiving diagnosis of the disease.

It is emphasized that the QoL data of the participants are evidenced by the mean and generalizes the behavior of adult cancer patients who undergo HSCT. However, patients view the health/illness process in different ways, meaning that some patients face reality with greater empowerment than others[22].

In this sense, the (nursing) team should be prepared to provide guidelines regarding doubts and fears throughout outpatient follow-up, minimizing the suffering related to the treatment. It is also necessary to implement an individualized care plan that focuses on the reality to be confronted, preparation for leaving the hospital environment and care during the outpatient period, aiming at autonomy of the individual and family participation in order to provide humanized and quality care[23-24].

Correlation of the presence of GvHD up to 100 days with absolute scores on general QoL of QLQ-C30 and global QoL of FACT-BMT demonstrated the significant relationship between the presence of GvHD with the pre-hospital discharge and 100 days post-HSCT periods.

A multicenter, prospective, observational cohort study conducted by the cGvHD consortium (chronic

graft-versus-host disease) with 481 patients presenting this complication evaluated the relationship between depression, anxiety, QoL, chronic GvHD and functional capacity. They concluded that patients with this complication reporting depression and anxiety had impaired QoL and functional capacity. Additionally, self-reported depression was associated with lower overall survival[25].

It should be noted that the variable GvHD in this study did not identify the affected organ/system and was correlated with the general and global QoL scores, which in turn reflect all domains of the implemented questionnaires. In this way, we can perceive the interference magnitude of this complication in the QoL of the patients after HSCT. Regardless of the characteristic of GvHD, we can state that it is predictive of worse QoL.

Another multicenter cohort study also coordinated by the cGvHD consortium with 522 patients correlated QoL assessed with the FACT-BMT of patients with chronic GvHD and age, observing that despite the lower physical fitness and functional capacity, patients with advanced age demonstrated preserved QoL and similar survival compared to younger patients[4].

In this context, it is important to emphasize that knowledge about the disease and its evolution allow for priorities to be established in relation to the care provided[26]. GvHD and its secondary complications are complex and it is important to highlight that the follow-up be performed by an outpatient multidisciplinary team in specialized HSCT centers[27].

As it is a peculiar complication of specific treatment, GvHD must be accompanied by a (nursing) team who are attentive to indications of complications and signs of improvement which may occur. We emphasize the importance of accurate and detailed attention given by the nurse, having an effective methodology for early observation of GvHD indicative signs through a directed physical examination during patient hospitalization.

In addition to observation and accurate reporting of symptoms, the frequency and intensity of symptoms should be investigated so that early interventions can be performed, as they are essential in the course and evolution of the complication. In order for GvHD to be handled correctly after it is detected, nurses need to have scientific and technical knowledge as well as human interdisciplinary skills. This study provides support for nursing to understand that the specific actions in patients with GvHD not only reach the symptoms but also impact on the QoL of these patients.

It should be considered that the etiology is in the inflammatory process, however consequences go beyond physical conditions. These patients have already experienced a diagnosis of cancer, and at present being afflicted with GvHD regresses their hope of survival, as it is known that morbidity and mortality rates increase. Thus, the already impressive physical complications are not the only ones that permeate the mental state of these individuals.

In being aware that GvHD affects all domains of QoL, it is necessary that nurses give attention to the resulting effects such as anxiety, social isolation due to the longer time of hospitalization and frequent readmissions, self-esteem related to body image disorder, and disruptions of normal sleep patterns due to the need for nocturnal interventions, among others.

Therefore, it is important to emphasize interdisciplinarity as an instrument for the advancing qualitative attention, QoL and patient satisfaction. In order to do this, the health professionals who evaluate the clinical, epidemiological and social aspects are essential in order to achieve an effective alternative to the biological model of care[26].

A limitation of this study is related to the sample size, since it is restricted to patients with hematologic cancer and not to the entire population that undergoes HSCT. This also makes it impossible to correlate QoL with allogeneic and autologous graft types, as well as sociodemographic characteristics.

CONCLUSION

The present study found that the QoL of the adult patient with hematologic cancer is altered as a result of HSCT, and that the presence of GvHD is predictive of worse results; a fact that is related to the severity of this complication and the potential to affect different organ and systems and have an impact on aspects other than physical afflictions.

Nursing inserted in a multiprofessional team has the potential to implement actions that improve the QoL of these patients, either by management and control of the symptomatology related to GvHD, or by stimulating subjective actions that improve their perception about themselves.

RESUMO

Objetivo: Avaliar a qualidade de vida de pacientes adultos com câncer hematológico nos 100 dias do transplante de células-tronco hematopoéticas e verificar se a variável doença do enxerto contra o hospedeiro é preditiva de piores resultados. **Método:** Estudo observacional, correlacional e quantitativo, com 36 participantes adultos, diagnosticados com câncer hematológico que se submeteram ao transplante de células-tronco hematopoéticas de setembro de 2013 a junho de 2015. **Resultado:** A média de idade foi 37 anos, 52,78% eram do sexo feminino, e 61,11% com diagnóstico de leucemia. Os escores de qualidade de vida demonstraram impacto significativo entre o pré-transplante e a pré-alta hospitalar e entre os 100 dias pós-transplante. A análise estatística entre os escores dos grupos com e sem doença do enxerto contra o hospedeiro evidenciou significância entre a presença desta complicação e piores resultados. **Conclusão:** A qualidade de vida é alterada em decorrência do transplante de células-tronco hematopoéticas, em especial nos pacientes que apresentam doença do enxerto contra o hospedeiro.

DESCRITORES

Qualidade de Vida; Transplante de Células-Tronco Hematopoéticas; Doença Enxerto-Hospedeiro; Enfermagem Oncológica.

RESUMEN

Objetivo: Evaluar la calidad de vida de paciente adultos con cáncer hematológico los 100 días tras el trasplante de células madre hematopoyéticas y verificar si la variable enfermedad del injerto contra huésped es predictiva de peores resultados. **Método:** Estudio observacional, correlacional y cuantitativo, con 36 participantes adultos, diagnosticados con cáncer hematológico que se sometieron al trasplante de células madre hematopoyéticas de septiembre de 2013 a junio de 2015. **Resultado:** El promedio de edad fue 37 años, el 52,78% eran del sexo femenino y el 61,11% con diagnóstico de leucemia. Los puntajes de calidad de vida demostraron impacto significativo entre el pre trasplante y la pre alta hospitalaria y entre los 100 días post trasplante. El análisis estadístico entre los puntajes de los grupos con y sin enfermedad del injerto contra huésped evidenció significación entre la presencia de esa complicación y peores resultados. **Conclusión:** La calidad de vida se modifica como consecuencia del trasplante de células madre hematopoyéticas, en especial en los pacientes que presentan enfermedad del injerto contra huésped.

DESCRIPTORES

Calidad de Vida; Trasplante de Células Madre Hematopoyéticas; Enfermedad Injerto contra Huésped; Enfermería Oncológica.

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