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Cognitive Impairment and Quality of Life of Patients Subjected to Hematopoietic Stem Cell Transplantation*

Theme: Chronic care, promotion and prevention.

Contribution to the discipline: The findings of this research evidence the importance of assessing the quality of life in patients with cancer with a focus on the multidimensionality of the construct, considering not only the physical aspects but also all the other domains that comprise it (cognitive, social, emotional, and functional). In this study, the cognitive function was assessed, and it was found that it changes during treatment and that it presents a positive correlation with the quality of life, which suggests that the greater the impairment of the cognitive function, the worse the overall quality of life.

ABSTRACT

Objective: To assess and correlate overall quality of life and the cognitive function of adult patients with hematologic cancer subjected to autologous and allogeneic hematopoietic stem cell transplantations up to three years after treatment. **Materials and method:** A longitudinal, observational, and analytical study was conducted with 55 patients in a reference hospital in Latin America, from September 2013 to February 2019, with the Quality of Life Questionnaire-Core 30, analyzed with the Spearman's correlation coefficient and Generalized Linear Mixed Model tests. **Results:** Overall quality of life in autologous and allogeneic transplantations presented a decline

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in the pancytopenia phase (59.3 and 55.3, respectively). There was impairment of the cognitive function in the autologous group in post-transplantation after two years (61.90) and, in the allogeneic group (74), in pancytopenia. In the autologous group, a positive (0.76) and significant ($p < 0.04$) correlation is observed between the cognitive domain and quality of life in post-transplantation after two years. In the allogeneic group, there was a positive (0.55) and significant ($p < 0.00$) correlation from 180 days after transplantation. **Conclusions:** Quality of life and the cognitive function present impairment and there is a correlation after the hematopoietic stem cell transplantation for both groups: autologous and allogeneic.

KEYWORDS (Source: DeCS)

Quality of life; cognitive dysfunction; hematopoietic stem cell transplantation; neoplasms, bone marrow transplant.

Disfunción cognitiva y calidad de vida de pacientes sometidos al trasplante de células madre hematopoyéticas*

RESUMEN

Objetivo: evaluar y correlacionar la calidad de vida general y la función cognitiva de pacientes adultos con cáncer hematológico sometidos al trasplante de células madre hematopoyéticas autólogo y alogénico hasta tres años luego del tratamiento. **Materiales y método:** estudio longitudinal, observacional y analítico con 55 pacientes, en un hospital de referencia en Latinoamérica, de septiembre del 2013 a febrero del 2019, con el instrumento Quality of Life Questionnarie-Core 30, analizado con las pruebas coeficiente de correlación de Spearman y el Generalized Linear Mixed Model. **Resultados:** la calidad de vida general en el trasplante autólogo y alogénico presentaron descenso en la fase de pancitopenia (59,3 y 55,3, respectivamente). Hubo disfunción cognitiva en el grupo autólogo posteriormente al trasplante dos años (61,90) y el grupo alogénico (74), en la pancitopenia. En el grupo autólogo, se observa correlación positiva (0,76) y significativa ($p < 0,04$) entre el dominio cognitivo y la calidad de vida en el post-trasplante dos años. En el alogénico, hubo correlación positiva (0,55) y significativa ($p < 0,00$) desde el post-trasplante 180 días. **Conclusiones:** la calidad de vida y la función cognitiva presentan compromiso y hay correlación luego del trasplante de células madre hematopoyéticas para ambos grupos, autólogo y alogénico.

PALABRAS CLAVE (Fuente: DeCS)

Calidad de vida; disfunción cognitiva; trasplante de células madre hematopoyéticas; neoplasias; transplante de médula ósea.

* El estudio es parte del proyecto temático "Calidad de vida de los pacientes con neoplasia hematológica sometidos al trasplante de células madre hematopoyéticas", que contó con el apoyo de la Coordinación de Perfeccionamiento de Personal de Nivel Superior de Brasil, bajo el n.º 88881.311846/2018-01, y de la Fundación Araucária y Universidade Federal do Paraná, convocatoria 15/2017.

Comprometimento cognitivo e qualidade de vida de pacientes submetidos ao transplante de células-tronco hematopoéticas*

RESUMO

Objetivo: avaliar e correlacionar a qualidade de vida geral e a função cognitiva de pacientes adultos com câncer hematológico submetidos ao transplante de células-tronco hematopoéticas autólogo e alogênico até três anos após o tratamento. **Materiais e método:** estudo longitudinal, observacional e analítico com 55 pacientes, num hospital de referência na América Latina, de setembro de 2013 a fevereiro de 2019, com o instrumento Quality of Life Questionnarie-Core 30, analisado com os testes coeficiente de correlação de Spearman e o Generalized Linear Mixed Model. **Resultados:** a qualidade de vida geral no transplante autólogo e alogênico apresentaram declínio na fase de pancitopenia (59,3 e 55,3, respectivamente). Houve comprometimento da função cognitiva no grupo autólogo no pós-transplante dois anos (61,90) e no grupo alogênico (74), na pancitopenia. Observa-se, no grupo autólogo, correlação positiva (0,76) e significativa ($p < 0,04$) entre o domínio cognitivo e a qualidade de vida no pós-transplante dois anos. No grupo alogênico, houve correlação positiva (0,55) e significativa ($p < 0,00$) a partir do pós-transplante 180 dias. **Conclusões:** a qualidade de vida e a função cognitiva apresentam comprometimento e há correlação após o transplante de células-tronco hematopoéticas para ambos os grupos, autólogo e alogênico.

PALAVRAS-CHAVE (Fonte: DeCS)

Qualidade de vida; disfunção cognitiva; transplante de células-tronco hematopoéticas; neoplasias; transplante de medula óssea.

* Este estudo faz parte do projeto temático "Qualidade de vida dos pacientes com neoplasia hematológica submetidos ao transplante de células-tronco hematopoéticas", que teve apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior do Brasil, sob o n.º 88881.311846/2018-01, e da Fundação Araucária e Universidade Federal do Paraná no Edital 15/2017.

Introduction

The advancement of cancer treatment technologies has considerably improved the chances of patient survival. However, it causes adverse effects in different systems of the organism and generates a negative impact on Quality of Life (QoL), which can last after the disease is cured (1, 2).

For hematologic cancers, hematopoietic stem cell transplantation (HSCT) represents a chance of increasing survival or even cure; however, it is at the same time a challenging treatment, with impacts on QoL domains and the patients' life experience (1). HSCT puts the patient at risk of cognitive impairment due to the use of chemotherapy at high doses, total body irradiation, and prophylaxis of chronic graft-versus-host disease. Adherence to treatment and the patient's QoL can be affected (3).

Cognitive impairment is a recurrent and little understood adverse effect of the chemotherapy and radiotherapy treatments, as well as of the disease itself. It is important to highlight that it can have late-onset and, in some patients, be progressive even years after ceasing therapy against cancer (2-4), particularly involving memory, concentration/attention, information processing speed, and executive functioning (5).

Cancer-related cognitive changes are a clinically relevant problem among adult patients, particularly after systemic treatment with chemotherapy. The potential consequences for the QoL of cancer survivors are significant and include issues related to overall, and emotional well-being, return to work and self-care ability (5, 6).

Despite the increasing number of research studies on this topic, the mechanism by which cancer and its treatment impact on the cognitive function have not been elucidated yet. Several researchers point out that cancer treatment can change the normal path of cognitive aging or even accelerate this mechanism through inflammatory processes, oxidative stress, and damage to the deoxyribonucleic acid (DNA) (6, 7). The loss of neural progenitor cells of the hippocampus is also considered a key mechanism for the cognitive impairment induced by cancer therapy. It is believed that the structural effects are mediated by the direct toxicity of the cell treatment, inflammation and oxidative stress (2, 8).

However, cancer-related cognitive impairment can have a multifactorial cause; in this context, different aspects must be considered, the type of treatment and the patients themselves among them (9). Its relationship with chemotherapy is little recognized and insufficiently treated (9). The increase in the number of cancer survivors and survival enhances the relevance of the concern about cognitive impairment and quality of life in these individuals.

Therefore, the objective of this study was to assess Overall Quality of Life (OQoL) and cognitive function impairment in adult patients with hematologic cancer subjected to HSCT up to three years after the treatment and to verify if there is a relationship between OQoL and the cognitive function in the monitoring stages and in the autologous and allogeneic transplantation modalities.

Materials and method

This is an observational, longitudinal, and analytical study, structured according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology initiative (better known as Strobe) (10), carried out in a hematopoietic stem cell transplantation service of a teaching hospital in the Brazilian South region, a reference in Latin America.

The non-probabilistic sample included 55 patients, considering the number of transplantations in the service from 2010 to 2012, with an addition of 50 % due to the the characteristic of the therapy with a high death rate evidenced by a number of authors (11).

The inclusion criteria were patients aged 18 years old or more, with a diagnosis of hematologic cancer and subjected to HSCT. Patients who did not present physical aptitude to fill in the questionnaires would be excluded; however, there were no such cases. The patients who withdrew their consent ($n = 0$), who evolved to death ($n = 28$), who did not attend the post-HSCT follow-up ($n = 5$), and who were subjected to a new HSCT ($n = 0$) during the study were discontinued.

Data collection took place from September 2013 to February 2019 in the hospitalization sector and the outpatient clinic of the hematopoietic stem cell transplantation service, in eight stages: pre-HSCT (to establish a baseline), pancytopenia period (between the seventh and tenth day after HSCT), pre-hospital discharge (between the twentieth and fortieth day after confirming medullary attachment), 100 days post-HSCT, 180 days post-

HSCT, 360 days post-HSCT, two years post-HSCT, and three years post-HSCT. To such an end, a sociodemographic and clinical questionnaire was used in the baseline stage to characterize the participants and, from 180 days onwards, another one to update the registration data and detect possible complications.

In all the data collection stages, the Quality of Life Questionnaire-Core 30 (QLQ-C30), version 2.0 was used, prepared by the European Organization for Research and Treatment of Cancer (EORTC), translated/validated for Brazil (12, 13), and authorized/availed via download directly to the researchers upon registration of the research project. QLQ-C30 consists of 30 items divided into functional scales (physical, emotional, cognitive, social functioning, and personal performance), a scale of symptoms/simple items, and OQoL, with scores expressed from 0 to 100. For the functional scale and OQoL, higher scores represent better QoL assessments (14). For this research, the values of the cognitive functioning scale and of OQoL were used.

The data obtained were tabulated in a Microsoft® Excel 2010 spreadsheet and analyzed and calculated according to the EORTC Scoring Manual (14) and using the STATISTICA 7.0 software. Descriptive analysis was performed with its results expressed as absolute and relative frequency values. For the analysis of the OQoL scores and of the cognitive function of QLQ-C30, Spearman's correlation coefficient was obtained. To assess associations between groups (autologous versus allogeneic), stages and possible group-stages interaction, the Generalized Linear Mixed Model (GLMM) was applied, using the SPSS 20 software.

In this research, GLMM was used for it enables the use of all the observations carried out since the beginning of the study. The measures do not need to be equally spaced and balanced, and the analyses can be conducted with data of individuals who were lost to follow-up or who presented a lack of information at some point in the study (15). The patients were considered as a random effect and as first-order autoregressive covariance matrix (AR1), with fit defined by the Akaike Information Criterion (AIC). The assumption of normality of residuals was verified by the QQ plot graph and the analysis of multiple paired comparisons was performed through the Sidak test.

This study has been approved by the Research Ethics Committee of the Health Sciences Sector of *Universidade Federal do Paraná*, Brazil, under opinion No. 411,548. After clarification of the research objectives, the individuals who agreed to participate in the study signed the Free and Informed Consent Form. To ensure the participants' anonymity, a sequential number (like 1, 2, 3...) was attributed to each of them as they were included in the study.

Results

Regarding the sociodemographic and clinical description, 55 patients were included in the study; of these, 33 (60 %) were discontinued during the first three years after HSCT (five [9 %] due to follow-up loss and 28 [51 %] due to death). There was a discrete prevalence of males, with 29 (52 %) subjects; 30 (55 %) stated being married or in stable unions and 27 (49 %) reported a family income of one to three minimum wages. In the sample, leukemia was the diagnosis with the highest occurrence, 36 (65 %), and 39 (71 %) were subjected to allogeneic HSCT.

The mean rates of HR-QoL in autologous and allogeneic HSCTs presented a decline in the pancytopenia phase (59.3 and 55.3, respectively), with relapse in the autologous group (63.1) two years after HSCT (Table 1).

Regarding the means of the QLQ-C30 cognitive function domain, higher impairment was observed in the autologous group two years post-HSCT (61.9) and, in the allogeneic group (74), in the pancytopenia period. When the Spearman's correlation coefficient between the cognitive function domain and OQoL was obtained, the results show that, in the autologous group, there was a positive (0.76) and significant ($p < 0.04$) correlation two years post-HSCT, which suggests that the lower the scores of the cognitive function domain, the worse the assessment of OQoL, that is, in this stage, there is impairment of the cognitive function, as well as of OQoL. In the allogeneic group, there was a positive and significant ($p < 0.00$) correlation starting from 180 days post-HSCT.

Figure 1 shows the evolution of the mean scores of OQoL and the cognitive function domain throughout time in the autologous group, with the worst mean value 2 years post-HSCT.

Figure 2 shows the evolution of the scores throughout the stages. In the allogeneic group, the worst mean of OQoL and of the cognitive function is observed in the pancytopenia stage, with the recovery of the baseline values from pre-discharge.

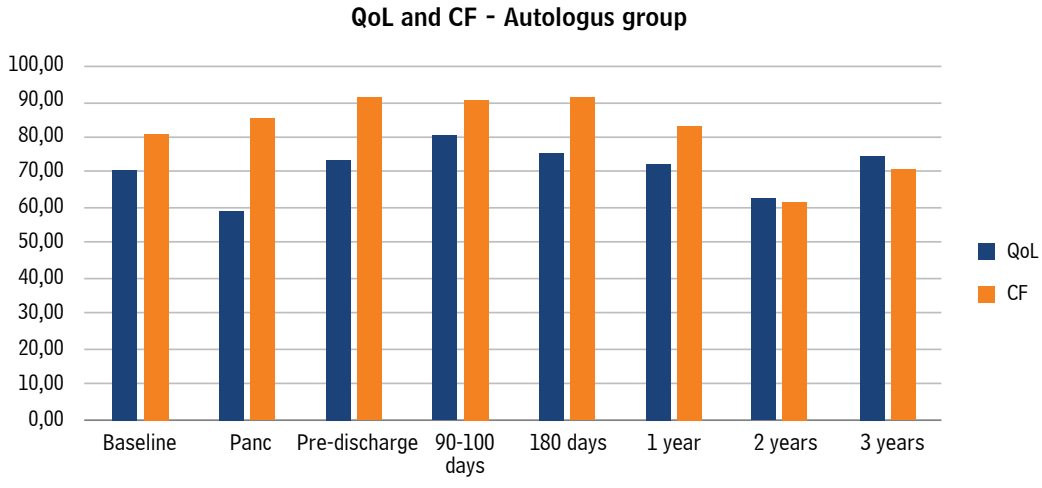
Table 1. Overall Quality of Life and cognitive function scores of the Quality of Life Questionnaire – Core 30 of the patients subjected to autologous and allogeneic transplantation and of the total group obtained in the eight research stages

Quality of Life Questionnaire — Core 30 (QLQ — C30)																
Scores	Pre-HSCT n = 55		Pancytopenia n = 50		Pre-discharge n = 49		Post-HSCT 100 days n = 41		Post-HSCT 180 days n = 38		Post-HSCT 360 days n = 32		Post-HSCT 2 years n = 25		Post-HSCT 3 years n = 22	
	Means SD		Means SD		Means SD		Means SD		Means SD		Means SD		Means SD		Means SD	
	Aut. n=16	Allo. n=39	Aut. n=16	Allo. n=34	Aut. n=16	Allo. n=33	Aut. n=13	Allo. n=28	Aut. n=12	Allo. n=26	Aut. n=11	Allo. n=21	Aut. n=7	Allo. n=18	Aut. n=4	Allo. n=18
OQoL	70.8 16.3	79.2 17.8	59.3 19.2	55.3 20.9	73.9 15.1	66.7 20.6	80.7 13.3	71.4 23.7	75.6 21.4	77.5 20.1	72.7 16.7	70.6 22.7	63.1 28.8	77.7 16.4	75.0 21.5	82.8 13.8
Cognitive function	81.2 18.3	84.1 21.9	85.4 19.1	74 16.6	91.6 18.2	83.3 24.6	91 12.9	82.1 29	91.6 11.2	80.7 21.9	83.3 23.57	80.9 28	61.9 36.9	84.2 25.8	70.8 25	82.4 23.2
Spearman Aut./Allo.	0.44	0.28	-0.24	0.24	0.11	0.27	0.46	0.03	0.33	0.55	0.55	0.58	0.76	0.61	0.73	0.88
p-value	0.08	0.08	0.37	0.16	0.67	0.11	0.11	0.86	0.29	0.00*	0.07	0.00*	0.04*	0.00*	0.26	0.00*
Spearman Total	0.33		0.12		0.27		0.14		0.49		0.55		0.74		0.82	
p-value	0.01*		0.37		0.05		0.38		0.00*		0.00*		0.00*		0.00*	

p-value: Statistical significance; HSCT: Hematopeic Stem Cell Transplantation; SD: Standard Deviation; Aut.: Autologous; Allo.: Allogeneic; OQoL: Overall Quality of Life; *: $p < 0.05$.

Source: Own elaboration.

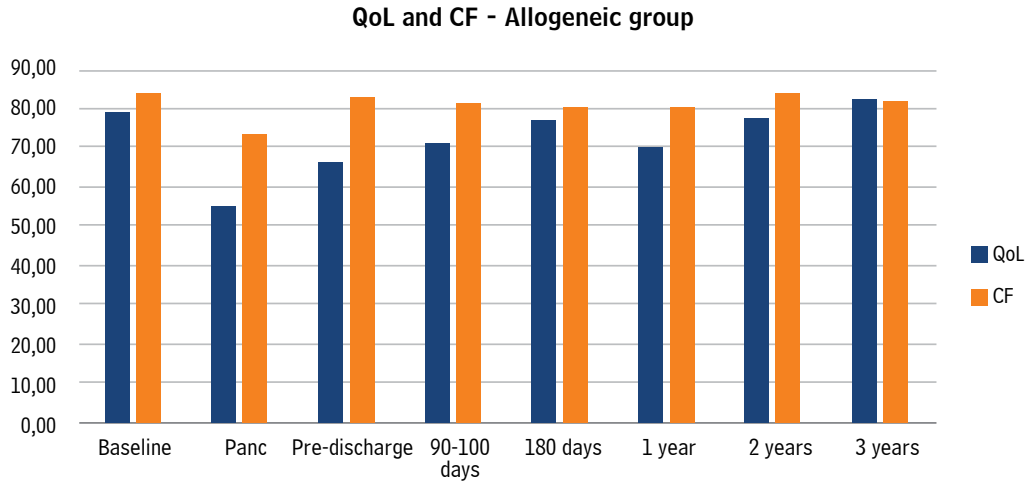
Figure 1. Quality of Life and cognitive function of the Quality of Life Questionnaire — Core 30 of the patients subjected to autologous and allogeneic transplantation in the eight research stages



QoL: Quality of Life; CF: Cognitive Function; Panc: Pancytopenia.

Source: Own elaboration.

Figure 2. Quality of Life and cognitive function of the Quality of Life Questionnaire — Core 30 of the patients subjected to allogeneic and allogeneic transplantation in the eight research stages



QoL: Quality of Life; CF: Cognitive Function; Panc: Pancytopenia.

Source: Own elaboration.

In the analysis of the evolution over time of the OQoL and cognitive function domain scores, GLMM was used and adjusted considering the patients as random effect. The best fit was defined by the AIC criterion = 2,678.89. The multiple paired comparisons performed by means of the Sidak test proved that the cognitive function score does not change over time, since OQoL presents a significant change across the stages.

Table 2 shows the results of the GLMM analysis for the group, stage, and group-stage interaction factors. A significant difference is observed across the stages for OQoL, with a change in the scores after the pancytopenia stage for both modalities.

Discussion

The diagnosis of severe disease and the indication of treatment with potential for cure, although with high mortality risk, impair the patients' QoL and the various domains that comprise it: physical, emotional, social, functional, spiritual, and cognitive. The health care team must be aware of the impairments that can occur due to the therapy chosen and, based on this information, promote the possible preventive and coping strategies to improve QoL and its domains.

Table 2. Mixed generalized linear model analysis of Overall Quality of Life and cognitive function between groups (autologous and allogeneic), stages (eight stages), and group-stage interaction

Type III test of the fixed effects				
Factors	OQoL**		Cognitive Function	
	F	p	F	p
Intercept	1.362.54	0.00	895.88	0.00
Groups	0.25	0.61	0.04	0.84
Stages	6.18	0.00*	1.63	0.12
Groups-stage	1.65	0.12	1.92	0.06

OQoL Overall Quality of Life; F: Snedecor statistics; p: statistical significance; *: $p < 0.05$.

Source: Own elaboration.

According to the Worldwide Network for Blood and Marrow Transplantation, over a million of HSCTs were performed worldwide, and approximately fifty thousand HSCT procedures are performed every year (16). These survivors run the risk of late effects that can adversely affect their QoL and increase morbidity and mortality. In this research, a high death rate is observed (51 %), characteristic of this treatment modality. A similar outcome (45.8 %) was found in a study that included 114,491 patients subjected to HSCT, which aimed to analyze the causes of death after HSCT over time (11). In Brazil, survival after autologous HSCT is 86 % in the first year and 77 % in the third year. For related allogeneic HSCT, 63 % and 53 %, and for unrelated HSCT, 58 % and 50 % in the first and third year, respectively (17).

In relation to the sociodemographic and clinical characteristics, a slight predominance of the male gender was observed (51 %). Regardless of gender, men and women share expectations and afflictions during the entire therapeutic path due to physical changes, social isolation and changes in the activities of daily living. Discomfort before the weaknesses perceived impairs QoL.

The mean age evidenced in this research was 36 years old. The age group of people who are on the rise in productive, family, social, and professional life stands out.

The diagnosis of aggressive disease and the treatment with potential to develop severe and risky complications result in concerns. There are feelings of fear and insecurity, mainly when the family member affected is the home provider, and their health condition interrupts their activities, even if partially, with the consequent reduction in income.

Regarding the data related to OQoL assessed with QLQ-C30, it was possible to observe that there are changes in both HSCT modalities. During the course from cancer diagnosis to survival, changes in QoL and in the cognitive function can occur; therefore, their identification is necessary as they represent complications with a high improvement rate when treated (18). A review study that aimed to determine the association between HSCT, anxiety, depression, and psychological quality found that the anxiety and depression rates were higher in HSCT survivors when compared to values of the general population. The presence of multiple complications and the patients' chronic conditions were important risk factors for deterioration in mental health (19).

Regarding the self-assessment of the cognitive function, it is observed that the scores are stable with satisfactory assessments, except for the autologous group two years post-HSCT, in which there is a decline in the mean value, with a positive and significant correlation. For the allogeneic group, a significant correlation was observed from 180 days onwards, which suggests that the higher the QoL impairment, the worse the cognitive function. Neurocognitive impairment, including symptoms such as memory dysfunction, impaired concentration, and difficulty in performing several tasks simultaneously, was recognized as a common complication in patients that are subjected to HSCT (20).

The cognitive function is complex and multi-determined. It is important to exhaust all risks and opportunities for improvement reflected in existing multimodal intervention approaches (21). Pre-, during, and post-HSCT neurocognitive assessments must be indicated to detect early possible deteriorations that may compromise OQoL. A mean of 15 % to 50 % of the patients with malignant tumors showed persistent cognitive impairment after chemotherapy (22). The mechanisms that lead to this are unknown; however, a number of studies point out that cognitive dysfunction before HSCT can result from the disease itself or from previous treatments. After HSCT, impairment can be associated with physical, emotional, and social decline, which can impact on adherence to the treatment and, consequently, on an increase in the risk of morbimortality (20).

In this research, there was a correlation between QoL and cognitive function in some stages, for both modalities, namely: autologous and allogeneic. In the analysis overtime carried out by means of the GLMM test, it was observed that there was a significant change in OQoL across the stages. In the cognitive function domain, there was not any significant change across stages, and groups, and even less in the group-stage interaction. The results for the cognitive changes in all types of cancer, except for those of the central nervous system, and the modalities of multiple treatments (chemotherapy, radiation, hormone therapy) point to multifactorial etiologies in addition to only the neurotoxicity of the chemotherapeutic agents. Stressful experiences have been postulated as a contributing factor for these cognitive changes (23).

A variety of problems hampers the ability to characterize and understand neurocognitive dysfunction after HSCT. In the first place, it is not clear if self-assessments of neurocognitive dysfunction are correlated with the results of objective neurocogni-

tive tests, and most of the studies do not include an analysis of the patients' perspectives. A study of correlations between the patients' perspective and the test results presented variations in relation to the return to work after transplantation, mentioning cognitive and health problems as the reason for the negative change in the functional domain, which included the ability to perform activities of daily living. The same study showed significant associations between the reports of cognitive impairment and younger age ($p = 0.02$), depressive mood ($p = 0.02$), anxiety ($p = 0.002$), and health-related QoL ($p = 0.008$) (24).

Cognitive decline and neurological changes associated with cancer diagnosis and treatment have been increasingly identified in a subgroup of patients (23). New research studies on the assessment of cognitive function and its impact on the course of the hematologic disease are necessary, not only during treatment but also in the survival period. Early detection strategies and coping interventions must be developed to control cognitive declines and, consequently, improve QoL during the treatment of hematologic cancer and in the survival period.

This research can contribute to the health professionals' practice regarding the reflection about the various domains that compose the QoL construct, as well as it evidences the need for the early assessment of the possible impairments, to promote actions that may prevent or reduce harms in QoL.

This is the first longitudinal evidence in which this change was shown; therefore, new research studies are suggested, with a focus on specific groups and populations, defining risk and protection factors, objective and subjective measures in which analyses of the patients' perceptions on the cognitive function are included. As a limitation, the research presents its sample size and the fact that it was conducted in only one transplantation center, which precludes generalization of the results.

Conclusions

It is concluded that the adult patients with hematologic cancer subjected to HSCT present OQoL impairment with the worst assessment in the pancytopenia period, in both modalities, namely: autologous and allogeneic. Regarding the cognitive domain, the worst assessment was observed two years post-HSCT for the autologous group and in the pancytopenia for the allogeneic group.

In this research, a correlation was observed between OQoL and the cognitive function for both HSCT modalities, which suggests that the higher the cognitive function impairment, the worse the OQoL of the patients subjected to HSCT. However, when the analysis of the relationship across groups (autologous versus allogeneic), stages and group-stage interaction, a significant relation was observed between the stages and OQoL. Regardless of that, knowledge about the changes that occur during the different post-HSCT stages can assist health professionals in improving the care provided, with a view to the multidimensionality of the QoL construct.

Conflict of interests: None declared.

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