

Hematopoietic stem cell retransplantation: concept analysis and development from Rodgers' evolutionary perspective

Retransplante de células-tronco hematopoéticas: análise de conceito e desenvolvimento da perspectiva evolutiva de Rodgers

Retrasplante de células madre hematopoyéticas: análisis y desarrollo de conceptos desde la perspectiva evolutiva de Rodgers

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Abstract

Introduction: Hematopoietic Stem Cell Retransplantation is the only treatment option for those who have developed graft failure in previously transplanted stem cells or who relapsed. Objective: To analyze and develop the concept of Hematopoietic Stem Cell Retransplantation from Rodgers' evolutionary perspective. Materials e methods: A documentary concept analysis study carried out from the six stages proposed by Rodgers. Data collection occurred by searching for articles in international databases. The studies were analyzed for the concept of Hematopoietic Stem Cell Retransplantation, its attributes, antecedents, consequents, substitute terms and related concepts. Results:

“Second transplant” and the related concept “Secondary graft” stood out as a substitute term. The most frequent attributes, antecedents and consequences were respectively: only option/treatment form for graft rejection or failure; graft failure; and increased survival. Conclusion: As a result, the concept of retransplantation was developed. Hematopoietic Stem Cell Retransplantation includes other purposes in addition to the new transplant and brings together different types of cell sources.

Keywords: Hematopoietic stem cell transplantation; Bone marrow transplantation; Concept formation; Graft rejection; Recurrence.

Resumo

Introdução: O retransplante de células-tronco hematopoéticas é a única opção de tratamento para aqueles que desenvolveram falha do enxerto em células-tronco previamente transplantadas ou que tiveram recidiva. **Objetivo:** Analisar e desenvolver o conceito de retransplante de células-tronco hematopoéticas a partir da perspectiva evolutiva de Rodgers. **Materiais e métodos:** Um estudo de análise de conceito documental realizado a partir das seis etapas propostas por Rodgers. A coleta de dados ocorreu por meio da busca de artigos em bases de dados internacionais. Os estudos foram analisados quanto ao conceito de Retransplante de Células-Tronco Hematopoéticas, seus atributos, antecedentes, conseqüentes, termos substitutos e conceitos relacionados. **Resultados:** “Segundo transplante” e o conceito relacionado “Enxerto secundário” destacaram-se como termo substituto. Os atributos, antecedentes e conseqüências mais frequentes foram respectivamente: única opção / forma de tratamento para rejeição ou falha do enxerto; falha do enxerto; e aumento da sobrevivência. **Conclusão:** Como resultado, o conceito de retransplante foi desenvolvido. O retransplante de células-tronco hematopoéticas inclui outras finalidades além do novo transplante e reúne diferentes tipos de fontes de células.

Palavras-chave: Transplante de células-tronco hematopoéticas; Transplante de medula óssea; Formação de conceito; Rejeição de enxerto; Recidiva.

Resumen

Introducción: El retransplante de células madre hematopoyéticas es la única opción de tratamiento para aquellos que han desarrollado falla del injerto en células madre previamente trasplantadas o que han recaído. **Objetivo:** Analizar y desarrollar el concepto de Retrasplante de Células Madre Hematopoyéticas desde la perspectiva evolutiva de Rodgers. **Materiales y métodos:** Estudio de análisis conceptual documental realizado a partir de las seis etapas propuestas por Rodgers. La recopilación de datos se realizó mediante la búsqueda de artículos en bases de datos internacionales. Los estudios fueron analizados por el concepto de Retrasplante de Células Madre Hematopoyéticas, sus atributos, antecedentes, consecuentes, términos sustitutos y conceptos relacionados. **Resultados:** “Segundo trasplante” y el concepto relacionado “Injerto secundario” se destacó como término sustituto. Los atributos, antecedentes y consecuencias más frecuentes fueron respectivamente: única forma de opción / tratamiento para el rechazo o fracaso del injerto; fracaso del injerto; y mayor supervivencia. **Conclusión:** Como resultado, se desarrolló el concepto de retrasplante. El retransplante de células madre hematopoyéticas incluye otros propósitos además del nuevo trasplante y reúne diferentes tipos de fuentes celulares.

Palabras clave: Trasplante de células madre hematopoyéticas; Trasplante de médula ósea; Formación de conceptos; Rechazo del injerto; Reparación.

1. Introduction

Hematopoietic Stem Cell Transplantation (HSCT) has been successfully used, however there are perceived risks of morbidity and mortality related to the procedure in its different phases (Liso et al., 2017; Lund et al., 2015). For success in this type of procedure, it is essential that infused cells proliferate in the recipient permanently to avoid rejection and that the new immune system received from the donor tolerates the recipient's tissues in order to prevent infections, graft versus host disease (GVHD) and other morbidities, which can be serious and even fatal (Hazar et al., 2012; Zago et al., 2012). In addition, the immune system must be functioning properly, and the disease stage, its complications, comorbidities at the time of transplantation and the healthcare offered during the entire process must also all be considered (Aversa et al., 2016).

Transplant failure is directly related to the procedure itself and is understood in this study as the failure of the performed transplant, represented by the interaction between the donor and recipient HLA systems, toxicity of the conditioning regime, acute or chronic GVHD, disease relapse or graft failure, which occurs in about 20% of patients (Zago et al., 2012).

HSCT failure can culminate in the need for a new transplant and will subject the patient to all stages of the procedure and to risks of morbidity and mortality. However, Hematopoietic Stem Cell Retransplantation (HSCR) maybe the only

treatment option for those who have developed graft failure in previously transplanted stem cells or who relapsed. Graft failure and relapse are considered to be one of the biggest complications and are associated with a poor prognosis, particularly in HPC recipients from alternative donors (Ayas et al., 2015).

The published studies on HSCR do not address in a clear and specific way this procedure and the whole process that involves it, leaving the reader and, especially, the health professional, in a way, confused about its real concept and also about how to determine its characteristics with regard to its goals (attributes), its indications (antecedents) and its results (consequent).

The standardization of language in the health area aims to offer not only sets of terms to certain specialties or professional praxis, but methodological references to support the structuring of semantic fields, documentary languages, teaching, assistance, management and research, which is important for the advancement of science in the most diverse areas of health.

Therefore, the concept of Hematopoietic Stem Cell Retransplantation requires better understanding so that incorporating its meaning contributes to standardizing semantic and scientific language in the health area in order to contemplate the clinical care, academic, management and research spheres.

In this sense, this study seeks to answer the following research question: How is the concept of Hematopoietic Stem Cell Retransplantation approached in the scientific literature? What is the contextual basis, substitute terms and concepts related to Hematopoietic Stem Cell Retransplantation according to Rodgers' evolutionary vision? Given the above, the objective is to analyze and develop the concept of Hematopoietic Stem Cell Retransplantation from Rodgers' evolutionary perspective.

2. Methodology

This is a qualitative study using the concept analysis technique carried out from the six steps proposed by Rodgers & Knafl (2000) in her evolutionary conceptual analysis model, namely: 1) definition of the concept of interest; 2) selection of the field for data collection; 3) highlighting the attributes of the concept and the contextual bases (antecedents and consequents); 4) analysis of the concept's characteristics (substitute terms and related concepts); 5) identification, if necessary, of a concept example; and 6) determining the implications of the concept.

To guide the research of studies in the databases, the integrative literature review was adopted as a methodological reference. To this end, the following steps proposed by Souza, Silva and Souza, Silva & Carvalho (2010) were followed: 1) elaboration of the guiding question; 2) searching the databases; 3) data extraction; 4) critical analysis of the studies included in the sample; 5) discussion of results; and 6) presentation of the review.

For the organization of the study and as a way of reaching stages 1 and 2 of the Rodgers conceptual model, a protocol was built to guide the searches, to develop the research and to check the scientific rigor that it requires. The search for studies was carried out in December 2019 using the following databases: SCOPUS; National Library of Medicine (PUBMED); Web of Science; Cumulative Index to Nursing and Allied Health Literature (CINAHL); and Science Direct.

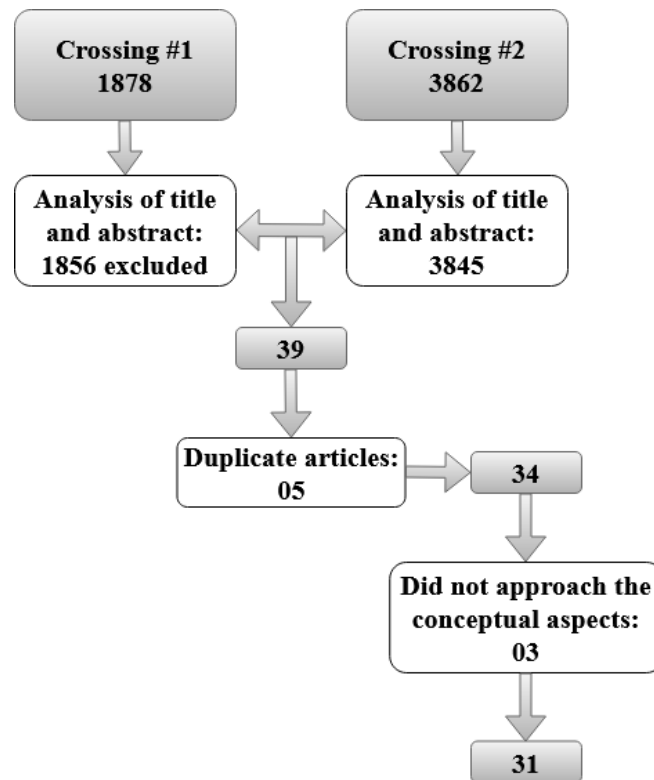
The following descriptors and their respective synonyms (Entry Terms) identified in the Medical Subject Headings (MeSH) were used to locate and select the studies, while AND and OR Booleans were used for the crossings without any type of filter, namely: crossing #1 - hematopoietic stem cell transplantation OR transplantation, hematopoietic stem cell OR stem cell transplantation, hematopoietic AND recurrence AND graft rejection OR transplant rejection OR transplantation rejection; crossing #2 - bone marrow transplantation OR transplantation, bone marrow OR grafting, bone marrow OR bone marrow grafting OR bone marrow cell transplantation OR transplantation, bone marrow cell AND recurrence AND graft rejection OR transplant rejection OR transplantation rejection. It should be noted that because it is an evolutionary analysis, there was no

temporal or language delimitation.

The inclusion criteria listed for the selection of articles were: complete studies available in the selected databases which address retransplantation in patients undergoing HSCT. Thus, articles that did not deal with retransplantation, reviews, meta-analysis, editorials, letters to the editor, abstracts, expert opinion, reviews, books, book chapters, theses, dissertations, monographs or course completion papers were excluded from the sample. In addition, duplicate studies were considered only once.

The electronic search process of studies in the databases retrieved a total of 5,740 articles, of which 31 were selected to compose the final sample of the concept analysis, as shown in Figure 1. Thus, 5,701 were excluded because they did not deal with Hematopoietic Stem Cell retransplantation, and 34 were chosen to read the full text, of which three were excluded for not addressing the conceptual aspects. Therefore, the final analysis sample was composed of 31 studies published between 1976 and 2018.

Figure 1 - Synthesis flowchart of the data collection process, Natal, RN, Brazil, 2019.



Source: Authors (2019).

The studies were analyzed using previously standardized indicators and related to the general characterization of the works, in addition to aspects aimed at conceptual analysis (steps 3 and 4 of the Rodgers & Knafl (2000) conceptual model).

The quantitative data were analyzed using simple descriptive statistics and the concepts were processed through the similarity analysis with the support of the Interface de R pour Analyses Multidimensionnelles de Textes et de Questionnaires (IRAMUTEQ) software program in order to identify the competition between words which resulted in the level of connection between them and their relationships (Marchand et al., 2013). The textual corpus was built from the elaboration of different abstracts after reading the complete files, which contained the indicators for conceptual analysis.

For this, it is essential to explore the size of the words and the thickness of the lines which join them, as these characteristics denote the significance of the terms to understand the analyzed phenomenon. However, the present study

proposes that the classic dichotomy between quantitative and qualitative be overcome during data analysis, as it enables the relationship between quantitative aspects related to similarity analysis and the essence of the words contained therein for the concept under study (Camargo et al. 2013).

3. Results and Discussion

The final sample for analysis consisted of 31 studies, of which 15 (48.39%) were observational longitudinal studies, 12 (38.71%) were reports/case studies, three (9.68%) were cross-sectional studies and one (3.22%) pilot study. All were published in international journals in the English language between the years 1976 and 2018, highlighting five studies (16.12%) published in 2012, 10 (32.26%) were developed in North America, 10 (32, 26%) in Europe, six (19.35%) in Asia and five (16.13%) were multicenter studies.

It is important to emphasize that for the discussion of the results, as well as in other sections, the articles comprising the final sample of the searches were mainly used considering that it is an evolutionary study, meaning the historical evolution of the HSCR concept. This fact justifies the use of studies which were published more than five years ago.

With regard to conceptual aspects, Table presents the main attributes, antecedents and consequences of the “Hematopoietic Stem Cell Replantation” concept which were pointed out by the investigated works. The antecedents and consequences of a concept are conditioned to a contextual basis, in this case the concept of HSCR. In addition, they maintain a relationship with the situational, temporal, sociocultural and disciplinary contexts of the profession at the present time Rodgers and Knafl (2000). The antecedents are considered phenomena which precede the investigated concept, while the consequences are situations resulting from the occurrence of the concept under study.

Table 1 -

Variable	(n=31)	%
Attributes		
Only option/form of treatment for graft rejection or failure	22	70.97
Only chance to increase survival	9	29.03
Antecedents		
Graftfailure	23	74.19
Graftrejection	14	45.16
Lowintensityconditioning regime	9	29.03
HLA differentiation	9	29.03
Diseaserecurrence	8	25.81
Opportunisticinfections	6	19.35
Numberofcellsinfused	4	12.90
T celldepletion	3	9.68
Pancytopenia	3	9.68
Donortype	3	9.68
Mixedchimerism	2	6.45
Typeofdisease	2	6.45
Spinal aplasia	2	6.45
Diseasestageat HSCT	1	3.22
HSCT with T cells	1	3.22
Consequences		
Increasedsurvival	19	61.29
GVHD	16	51.61
Toxicity associated with the conditioning regime	7	22.58
Mortality	6	19.35
Complete chimerism	5	16.12
Remissionofthedisease	3	9.68
Bleeding	2	6.45

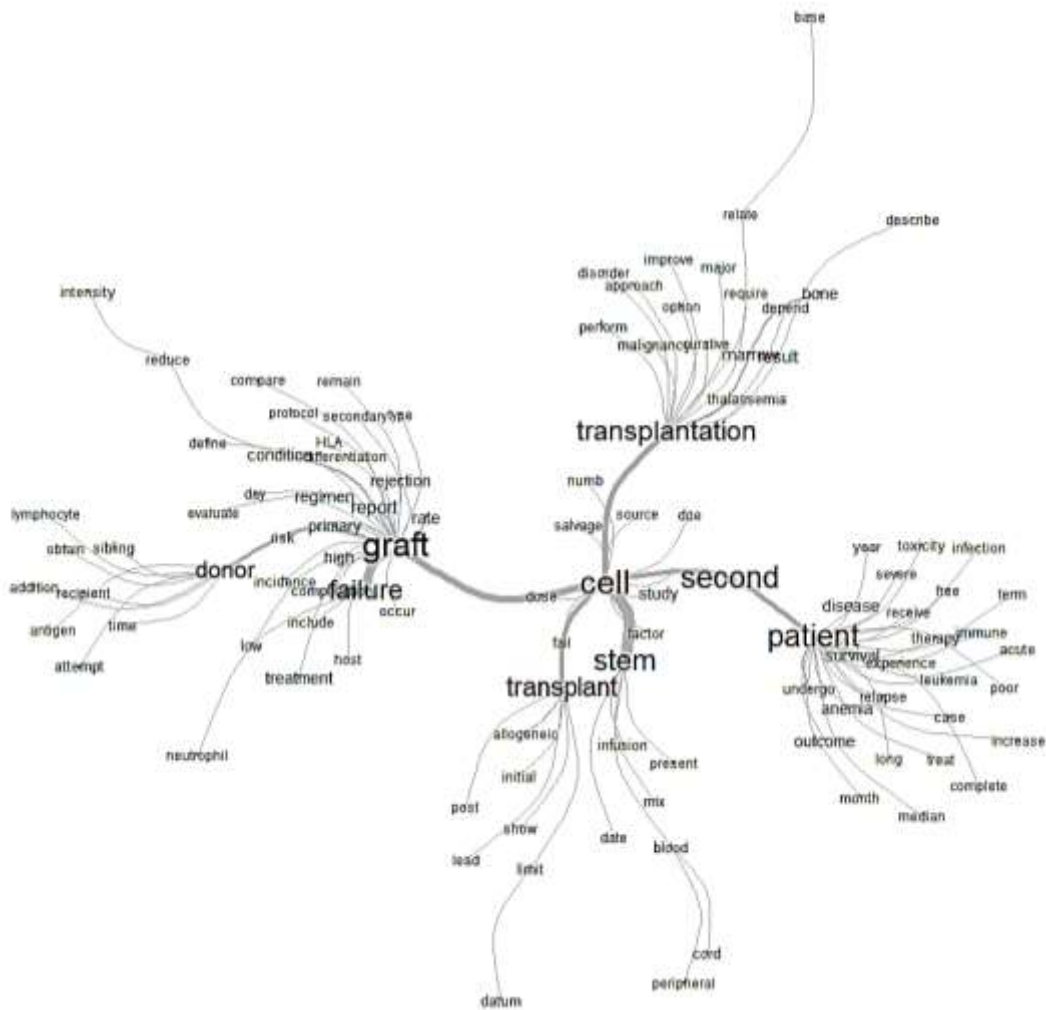
Abbreviations: GVHD, Graft versus Host Disease; HLA, Human Leukocyte Antigens; HSCT, Hematopoietic Stem Cell Transplantation. Source: Authors.

Two substitute terms were found referring to retransplantation, with emphasis on the terms “Second Transplant” found in 29 (93.54%) studies, and “Third Transplant” in two other (6.45%) researched articles. Regarding related concepts, the terms “Secondary Graft” were identified in four (12.90%) studies and “New Transplant” in two (6.45%).

In order to establish the fifth stage of the Rodgers & Knafl (2000) conceptual model, a similarity analysis was carried out with the support of IRAMUTEQ (Figure 2), with emphasis on the following terms: second, transplantation, transplant, stem, cell, graft, failure, patient and donor. Through this graph, it is possible to observe the occurrence of words and the connection between them in order to assist in identifying the content structure of a textual corpus and consequently of the concept itself, in addition to understanding the importance and strength of the connection between words. The word cell is centrally located and is linked to the other branches of the graph, as it is the basis of the HSCR, and represents the raw material of the procedure.

The importance of the antecedents and consequences inherent to the HSCR concept is highlighted and complement the similarity analysis as: reduced intensity conditioning regime, differentiation HLA and survival.

Figure 2 - Similarity analysis of the HSCR concept. Natal, RN, Brazil, 2019.



Fonte: Authors (2019).

According to the reading and analysis performed in this context, it can generally be inferred that the researched articles presented information inherent to the HSCR process from the procedure and treatments instituted to the reasons for graft failure or rejection. However, none of the studies presented a structured concept that would define retransplantation. Hence there is a need to develop a concept that characterizes and represents the procedure with content which incites an abstract mental image, notion or idea understood through the proper words used.

Thus, the HSCR concept developed through this study can be defined as “the only option/form of treatment for rejection, graft failure or relapse with a chance of increasing survival or promoting remission of the disease in patients who have undergone a previous HSCT”.

A clinical case was subsequently constructed to elucidate this concept and reach stage 6 of the Rodgers conceptual model based on experiences lived in a healthcare service and based on theoretical-scientific references to demonstrate the applicability of the HSCR concept.

Model case built to reach the fifth stage proposed for Rodgers evolutionary concept analysis: WHG, 13 years old, male, brown, single, catholic, student, accompanied by parents, born and resident of a city in the interior of the state, admitted to the Bone Marrow Transplant (BMT) sector with a diagnosis of Aplastic Anemia (ICD-10: D61.3) to undergo related allogeneic HSCR. The mother reported that the patient began to show frequent pancytopenia, fatigue, weakness, fever without

signs of infection and bleeding gums and nose about 110 days after the transplant. After evaluating and performing a new myelogram and spinal biopsy, previous graft failure was found due to HLA incompatibility, spinal aplasia and the need for HSCR with the aim to increase survival or achieve remission of the disease. Parents and patient were instructed on hospitalization, new conditioning regimen with greater intensity, mobilization of hematopoietic progenitor cells in the new donor (brother) and post-transplantation treatment.

The concept of HSCR is not yet well established in the health literature when it is possible to identify other words/expressions which are capable of representing it and explaining its attributes. In view of this assumption, it is considered relevant to clarify that substitute terms denote similar meanings to the HSCR concept; however, they are not robust enough to contemplate its meaning.

According to the researched studies, the most used substitute term was “Second Transplant”, followed by “Third Transplant”. Such terms can be considered synonyms for the scientific language because they have a semantic connection with the HSCR. Thus, when indicated, the patient will receive an HSCR as a treatment option for graft failure or rejection or as an opportunity to increase their survival (Korula et al. 2018).

The antecedent factors have a direct correlation of cause and effect with the HSCR concept. The main antecedents identified for the retransplantation to occur are graft failure, graft rejection, reduced intensity regimen, HLA differentiation, and disease recurrence, among others. This correlation is not a mere coincidence, it is intrinsic and inherent to the retransplantation process which will be indicated if any of these antecedents occurs.

The consequences are related to the antecedents and must follow them. Thus, the consequences presented in Table 1 are the result of the HSCR. The increase in survival was the most frequently pointed out consequence and is the desired result we want to achieve as part of this process. GVHD was the second most indicated consequence, and this is an unwanted complication to HSCT, as it brings with its morbidity and chance of mortality for the re-transplanted patient.

Toxicity related to the conditioning regimen is expected for all patients and presents itself differently for each individual with episodes of nausea, vomiting, diarrhea, mucositis, headache, tremors, bleeding, among others (Ministério da Saúde, 2008).

The first allogeneic Bone Marrow Transplant (BMT) was performed by Edwar Donnall Thomas in 1957, with subsequent worldwide expansion from that point onwards when the procedure received new indications, as well as constituting a treatment option for acute leukemia and aplastic anemia.

It currently encompasses therapy for congenital disorders of the hematopoietic system, metabolic disorders, autoimmune diseases, and type I diabetes, among others. The use of unrelated donors with HLA differentiation is a viable possibility and increases the chances of allogeneic transplants (Walters, 2015). In addition, the term BMT was replaced by HSCT, since other sources of hematopoietic stem cells were discovered such as peripheral blood and umbilical cord and placental blood (Hornberger et al. 2019).

However, primary graft failure after HSCT is a life-threatening complication and its main causes are allogeneic transplantation with an unrelated or alternative donor, graft rejection, donor with HLA differentiation, or a reduced intensity conditioning regime, among others (Lund et al., 2015; Aversa et al., 2016; Fuji et al. 2012; Onishi et al., 2017).

Research on bone marrow retransplantation was initiated between the 1960s and the 1970s in patients who had anterior graft failure or rejection. The term HSCR refers to a subsequent transplant after a negative result of primary autologous or allogeneic HSCT. There are several terms used to refer to HSCR, among them: second transplant, new transplant, secondary graft, rescue, reinfusion, among others (Onishi et al., 2017). However, failure of the second and third grafts may occur in some patients.

It is possible to observe the evolution of the HSCR concept over the years. In the beginning, it was called “bone

marrow retransplantation”, following the procedure with the only source of hematopoietic stem cells known at the time (Meuwissen et al., 1976). Then it received the name “second hematopoietic stem cell transplant” Ayas et al., (2015) and Ikeda et al. (2016), but this designation does not include the scope of the treatment since some patients may present rejection of the second graft and need a third transplant. Thus, the term HSCR becomes the most appropriate to justify the current concept.

HSCR is considered the only treatment option/form and the only chance to increase survival for patients who developed rejection or failure of the previous graft (Lund et al., 2015; Ayas et al., 2015; Kedmi et al. 2009. The recipient will undergo a reassessment and must meet the eligibility requirements for grafting the new marrow. There is no predetermined time for the HSCR performance, but it is generally performed in patients more than three months after the first HSCT (Lemaistre et al., 2013).

As positive consequences of this process, we can point to increased post-transplant survival, disease remission and complete chimerism. A Japanese study of 220 patients undergoing HSCR after primary graft failure resulted in a 58% survival rate for patients who received umbilical cord and placental blood cells, 38% for bone marrow transplant recipients and 28% for those who received peripheral blood cells (Fuji et al., 2012).

One of the biggest negative consequences of HSCR is the high mortality rate related to the procedure when infection is the most frequent cause. Many patients have organ toxicity related to the conditioning regime and infections due to prolonged pancytopenia or neutropenia during this period (Park et al., 2014).

Case studies have been (and still are) produced over the decades with the aim of researching and reporting the events arising from the HSCR process. Such publications address aspects related to graft failure or rejection, the type of disease, the conditioning regimes used, the type of donor, the presence of GVHD and especially the consequences such as survival, disease remission and chimerism(Lemaistre et al., 2013; Meuwissen et al.,1976; Ikeda et al., 2016; Blau et al., 1999; Byrne et al, 2001; Choeyprasert et al., 2012; Eapen et al., 1999; Fernandes et al. 2007; Gmür et al., 1979; Medeiros et al., 2001; Wiesmann et al,2003; Wolff et al, 1998).

In summary, HSCR is the procedure for grafting hematopoietic stem cells from bone marrow, peripheral blood or umbilical cord and placental blood, performed specifically after failure or rejection of the previous graft, which aims to increase disease-free survival, remission or cure the underlying disease.

Construction of the HSCR concept implies scientific development and standardizing language in the health area, which offers a solid basis for understanding the therapeutic method under study and anchored in its antecedents and consequences. The proposal for a reflective-theoretical foundation of this research came from the point of view of the complexity of the retransplantation concept and when talking about the immersed subject, which has a most particular and unique perceptual experience of such a process.

4. Conclusion

An effective understanding of the use and application of the constructed HSCR concept is expected in order to guide the development of this relevant treatment being disseminated in the health area. In addition, this conceptual analysis can favor standardizing the use and meaning of the concept by researchers in different knowledge areas.

This study enabled us to understand the multiple interfaces of the hematopoietic stem cell retransplantation concept in order to elucidate its similarities, differences and relationships. It was concluded that the HSCR includes other purposes in addition to the second transplant, such as increasing patient survival and remission of the underlying disease and bringing together different types of cell sources.

The results covered in this study may significantly contribute as a subsidy to improve and apply in standardizing scientific language in the health area in view of the importance of constant qualification and scientific updating, which must be

based on evidence which best meets the needs of researchers and healthcare professionals.

A limitation of this study can be attributed to the fact that the research was only conducted in international electronic databases to the detriment of research in course completion works, books and other sources of literature. However, the study answered the research questions. Therefore, broader studies are important when considering the evolution of the concept over time.

Concept analysis-type studies are considered important for the growth of the body of knowledge in nursing and in the health area, as they signal a logical and systematic organization of conceptions. This process contributes to the advancement of theoretical knowledge in nursing and health. Furthermore, it is necessary to develop other studies of a quantitative and/or qualitative nature that investigate the HARTH in order to apply its concept so that it becomes a standard among the standardized language in health services.

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