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## **PROTOCOL OF NURSING CARE ON ZERO DAY OF THE TRANSPLANTATION OF HEMATOPOETIC STEM CELLS: COLLECTIVE CONSTRUCTION**

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### **ABSTRACT**

**Objective:** to construct a protocol of nursing care to the patient on day zero of hematopoietic stem cell transplantation.

**Method:** a convergent care research was developed from August to December 2016 in a Bone Marrow Transplant Service. The participants were twenty-two nurses from this service. The technique of data collection used was discussion groups. For the analysis the following steps were taken: transcription of the data, highlighting the suggestions of the participants; distribution of contributions by theme, for synthesis of the elements in a coherent whole, scientific evidence and contributions of the participants; and construction of the protocol, with refinement and approval of the final version by nurses.

**Results:** the protocol, guides nursing care to be provided by the nurse on day zero of hematopoietic stem cell transplantation, according to the infusion mode: fresh and cryopreserved-thawed. These precautions aim to prevent, identify and intervene early in complications related to cell infusion.

**Conclusion:** the protocol, product of the research, was elaborated in the union of scientific evidences, with the reality of the service and the experience of the participating nurses. The utilization of the methodological steps of convergent care research was a facilitator, because, as it presupposes, it provided the union of care practice with scientific research. The participation of nurses in the construction and approval of the protocol enabled the subsequent implementation and use of this tool in nursing service.

**DESCRIPTORS:** Nursing. Nursing care. Hematopoietic stem cell transplantation. Hematopoietic stem cells. Nursing assessment. Protocols.

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# PROTOCOLO DE CUIDADOS DE ENFERMAGEM NO DIA ZERO DO TRANSPLANTE DE CÉLULAS-TRONCO HEMATOPOÉTICAS: CONSTRUÇÃO COLETIVA

## RESUMO

**Objetivo:** construir um protocolo de cuidados de enfermagem ao paciente no dia zero do transplante de células-tronco hematopoéticas.

**Método:** trata-se de pesquisa convergente assistencial, desenvolvida de agosto a dezembro de 2016 em um Serviço de Transplante de Medula Óssea. Os participantes foram vinte e dois enfermeiros deste serviço. A técnica de coleta de dados utilizada foi grupos de discussão. Para a análise seguiu-se as etapas: transcrição dos dados, com destaque das sugestões dos participantes; distribuição das contribuições por temática, para síntese dos elementos num todo coerente, evidências científicas e contribuições dos participantes; e construção do protocolo, com refinamento e aprovação da versão final pelos enfermeiros.

**Resultados:** o protocolo orienta os cuidados de enfermagem a serem prestados pelo enfermeiro no dia zero do transplante de células-tronco hematopoéticas, conforme a modalidade de infusão: fresca e criopreservada-descongelada. Estes cuidados visam prevenir, identificar e intervir precocemente nas complicações relacionadas à infusão das células.

**Conclusão:** o protocolo, produto da pesquisa, foi elaborado na união de evidências científicas, com a realidade do serviço e a experiência/vivência dos enfermeiros participantes. A utilização dos passos metodológicos da pesquisa convergente assistencial foi um facilitador, pois, como pressupõe, proporcionou a união da prática assistencial com a pesquisa científica. A participação dos enfermeiros na construção e aprovação do protocolo possibilitou a posterior implantação e utilização deste instrumento no serviço de enfermagem.

**DESCRIPTORIOS:** Enfermagem. Cuidados de enfermagem. Transplante de células-tronco hematopoéticas. Células-tronco hematopoéticas. Avaliação em enfermagem. Protocolos.

# PROTOCOLO DE CUIDADOS DE ENFERMERÍA EN EL DÍA CERO DEL TRANSPLANTE DE CÉLULAS MADRE HEMATOPOÉTICAS: CONSTRUCCIÓN COLECTIVA

## RESUMEN

**Objetivo:** construir un protocolo de cuidados de enfermería al paciente en el día cero del transplante de células madre hematopoyéticas.

**Método:** se trata de una investigación convergente asistencial, desarrollada de agosto a diciembre de 2016 en un Servicio de trasplante de médula ósea. Los participantes fueron veintidós enfermeros de este servicio. La técnica de recolección de datos utilizada fue grupos de discusión. Para el análisis se siguieron las etapas: transcripción de los datos, con destaque de las sugerencias de los participantes; distribución de las contribuciones por temática, para síntesis de los elementos en un todo coherente, evidencias científicas y contribuciones de los participantes; y la construcción del protocolo, con refinamiento y aprobación de la versión final por los enfermeros.

**Resultados:** el protocolo, orienta cuidados de enfermería a ser prestados por el enfermero en el día cero del transplante de células madre hematopoyéticas, según la modalidad de infusión: fresca y criopreservada-descongelada. Estos cuidados tienen como objetivo prevenir, identificar e intervenir precozmente en las complicaciones relacionadas con la infusión de las células.

**Conclusión:** el protocolo, producto de la investigación, fue elaborado en la unión de evidencias científicas, con la realidad del servicio y la experiencia / vivencia de los enfermeros participantes. La utilización de los pasos metodológicos de la investigación convergente asistencial fue un facilitador, pues, como presupone, proporcionó la unión de la práctica asistencial con la investigación científica. La participación de los enfermeros en la construcción y aprobación del protocolo posibilitó la posterior implantación y utilización de este instrumento en el servicio de enfermería.

**DESCRIPTORES:** Enfermería. Cuidados de enfermería. Trasplante de células madre hematopoyéticas. Células madre hematopoyéticas. Evaluación en enfermería. Protocolos.

## INTRODUCTION

The hematopoietic stem cell transplantation (HSCT) is characterized as a therapy used to achieve a long period of remission or cure for patients with benign or malignant hematological disorders.<sup>1</sup> It is a long therapeutic process that can be divided into three distinct phases: pre, trans and post-HSCT.<sup>1-2</sup>

The trans phase is essential for successful treatment and corresponds to day zero, in which hematopoietic stem cells (HSCs) or hematopoietic progenitor cells (HPCs) are infused into the patient or recipient, which, after the medullary engraftment, promote reconstitution hematopoietic and immunological systems. The HSCs may arise from bone marrow, peripheral blood, or placental umbilical cord blood. They can be infused fresh, or cryopreserved, after thawing, thus constituting two infusion modalities.<sup>2</sup>

Although the literature does not specify the professional who performs the infusion of HSCs,<sup>3</sup> in Brazil, the nurse is legally qualified for this function, in accordance with Resolution No. 200/1997 of the Federal Nursing Council (COFEN).<sup>4</sup> In 2016, there was revision and updating, with the publication of Resolution No. 511/2016, however, this does not address the performance in HSCT, only in hemotherapy.<sup>5</sup>

At day zero the nurse is responsible for the infusion activity of HSCs and for a range of care, such as preparation of material and equipment, patient monitoring, administration of medications prescribed by the physician, performed before, during and after the infusion.<sup>3,6-7</sup> Therefore, it should be prepared in order to prevent, identify and intervene in complications related to the procedure.<sup>6-8</sup>

Although it is a relevant topic for nursing, especially for professionals working on HTCT services, there are gaps in knowledge regarding specific care for day zero, especially in the national setting. One example is the integrative literature review, which aimed to identify and characterize the national scientific production of Nursing in HSCT. 29 publications were found and of these, one was related to the nurses' performance on day zero.<sup>9</sup>

One of the ways of performing effective interventions in complex settings, such as in HSCT, is through the use of particular protocols.<sup>8</sup> This is also a recommendation of the Foundation for Accreditation of Cellular Therapy (FACT): to have written policies on the administration of cell therapy products, the category in which the HSCs are classified.<sup>10</sup> In this context, the proposal for the construction of a nursing care protocol on day zero of HSCT emerged.

Instruments containing structured recommendations were systematically considered as protocols. These are based not only on scientific evidence, but also consider the technological and economic evaluation of health services, aiming to guarantee their quality. One of the purposes of these instruments is to guide the decisions of health professionals about appropriate care, whether in disease prevention situations, or in the recovery or rehabilitation of health.<sup>11-12</sup>

It is pointed out as positive results in the use of nursing protocols the reduction of the variability of care actions, improvement in the qualification of professionals for care decision making and care innovation. One of the determining factors for the success in the implementation of these instruments is the involvement of professionals who will use them in their construction process.<sup>12</sup>

One of the research methods that advocates the involvement of professionals in the construction process of these instruments is the Convergent Care Research.<sup>13</sup> Thus, this method has been widely used in research that involves the construction of protocols. A study that aimed to focus the methodological pathway used by Brazilian researchers in the area of nursing, for the construction and validation of protocols, found as a result, among 24 postgraduate studies, in a period of thirteen years, seven dissertations that used Convergent Care Research in the construction and validation process of

these instruments. Furthermore, this study also found that the most common step in the construction of protocols, besides reviewing the scientific literature, was the participation of professionals to assist in this process.<sup>14</sup>

Given the specificity of nursing care in HSCT, especially on day zero, and the need to use protocols to organize and systematize it, the question that guided this study was: What care is needed to compose a nursing care protocol on day zero of HSCT? And the objective of the research was to construct a nursing care protocol to the patient on day zero of HSCT.

## METHOD

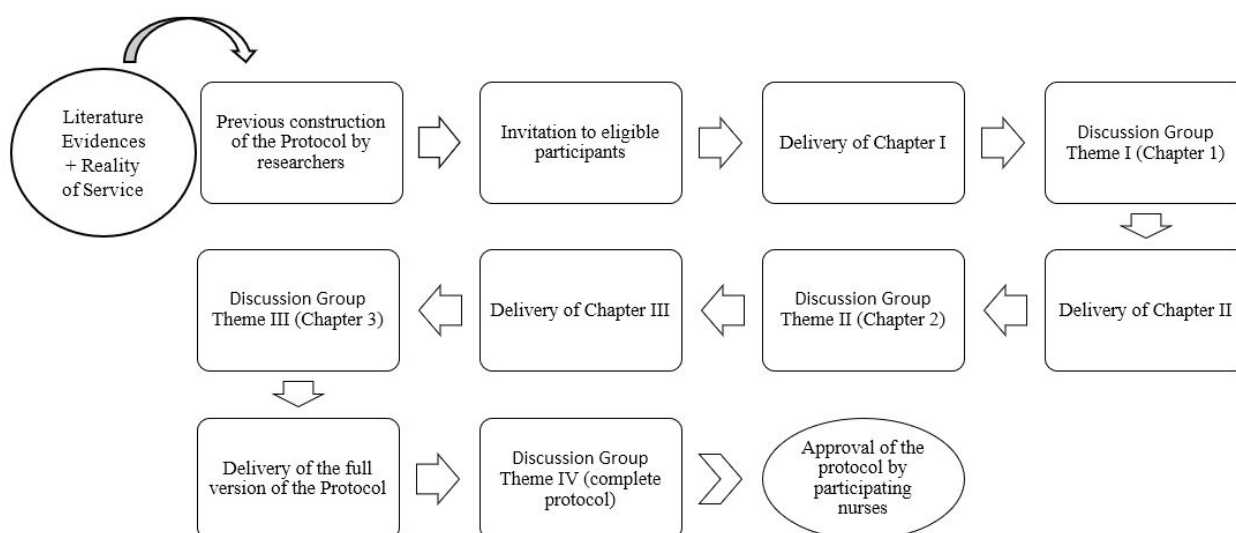
It is a Convergent Care Research, characterized by the property of making the convergence of research actions and health care actions, thus enabling the development of knowledge aimed at minimizing problems, introducing innovations and changes in the context of care practice.<sup>13</sup> It is implemented in four stages, namely: conception, instrumentation, screening and analysis.<sup>15</sup>

At the conception stage, the guiding question and the purpose of the study were constructed, addressed in the Introduction topic of this manuscript. The search for sources of knowledge in the literature was also started.

In the instrumentation stage were defined the physical space, the research participants and the methods/techniques for collecting the information. The survey was conducted in the Inpatient care Unit of a Bone Marrow Transplant Service (STMO), from a university hospital in the southern region of Brazil. For the selection of participants, the following inclusion criteria were established: being an assistant nurse or Nursing manager, filled in the STMO Inpatient care Unit; have at least two years of experience in HSCT; and the criterion of exclusion: being on leave of absence for health treatment, maternity leave or other. The technique of discussion groups was defined to unite the experiences of nurses relating to zero-day care. It is through this technique that the researcher establishes a way of access that allows him to analyze the collective opinion of the group.<sup>16</sup> The discussion groups were recorded, with authorization, and later analyzed.

The stage of investigation corresponded to the construction of the protocol. Between the months from August to October 2016, the protocols were prepared in advance by the researchers, based on evidence from the literature added to the reality of the service. And from October to December 2016, in the discussion groups, the nurses contributed suggestions and criticisms, in the refinement of the protocol.

To optimize the contribution of nurses, 15 days before each meeting, the protocol chapter previously prepared for previous reading was printed. The discussion groups were divided into four themes. For each theme, seven meetings were held (two in the morning, two in the afternoon and three in the evening), totaling 28 discussion groups, lasting 30 to 60 minutes each. Figure 1 synthesizes the screening stage.



**Figure 1 - Synthesis of the screening stage**

In this stage, the participants were characterized by filling in an instrument containing items such as gender, age, professional training time and time of experience in the area of HSCT and postgraduation data.

For the fourth and last phase of the Convergent Care Research, analysis, the following steps were carried out: transcript of Groups discussions (I, II, III and IV), in original file, in program *Microsoft Office Word 2016*; reading and distribution of thematic contributions, divided into pre-established chapters: Chapter I - Introduction, Chapter II - Fresh Hematopoietic Stem Cells, Chapter III - Cryopreserved-thawed hematopoietic stem cells; and, refinement of the protocol, with approval by the nurses, of the final version. During the process of analyzing the data, the anonymity was guaranteed with the use of codes to identify the participants, using the letters "ED", followed by numbers. Chart 1 presents two examples of this stage.

**Chart 1 - Examples of the analysis stage. Curitiba, PR, 2016**

Chapter of the Protocol	Version elaborated by the researcher	Contributions of nurses in the discussion groups	Version approved by nurses
Chapter 2	Homogenize the Hematopoietic stem cells bag.	When and how often will it be done? (ED1, ED2, ED4, ED13).	Homogenize the Hematopoietic stem cells bag and check the drip speed during infusion every one hour.
Chapter 3	Program the infusion of each bag (can be one or more bags) for 15 to 20 minutes.	Would not it be better to approach that this time is independent of the way the cells are thawed? (ED1, ED2, ED8, ED21). It would not be better to put the flow in ml/min, because the volume may vary (ED1). And when the cells do not infuse gravitationally? I suggest putting the option in bolus (ED2, ED6, ED7, ED18, ED21).	Program the infusion of each bag (it can be one or more bags) at a speed of 10ml/minute, regardless of the way of thawing (bedside, dilution or washing). Start the infusion slowly and schedule the end to the calculated time if the patient tolerates well.  This infusion time should also be respected in cases of use of syringe and three-way device.

## RESULTS

Twenty-one nurses who worked in the care and one in the STMO Nursing Office participated, being 21 females and one male. The participants had between five and 33 years of training and the time of experience in the area of HSCT ranged from two to 31 years. Of the 22 participants, ten had training/updating courses to work in the function and 21 had completed specialization, and for two the subject was related to HSCT area. Five of the 22 participants were masters, four with theme matter related to the area and nine with masters in progress, all of them related to the area of HSCT.

The number of participants in the discussion groups ranged from 15 to 22 per meeting. Chart 2 presents the objectives of each discussion group and the number of participations.

**Chart 2** - Objectives of the discussion groups and attendance of participants.  
Curitiba, PR, Brazil, 2016

Discussion group	Objectives	Number of participants
I	Present the research in detail; Present the format intended for the protocol; Discuss the Protocol Introduction (Chapter 1).	22
II	Collectively define nursing care before, during and after infusion of fresh Hematopoietic stem cells bag (Chapter 2).	18
III	Collectively define nursing care before, during and after infusion of cryopreserved-thawed Hematopoietic stem cells bag (Chapter 3).	19
IV	Present the final version of the Protocol (complete, with the 3 chapters) and propose the approval of the Protocol by the participants.	15

In the fourth and last discussion group the final version of the protocol was presented, a result of the version previously elaborated by the researcher, added to the contributions of the nurses. This version consists of 44 pages, distributed in three chapters. Chapter 1 was the Introduction that addresses topics such as definition, types and stages of HSCT; sources of HSC; compatibility of the blood type (ABO system) in HSCT; preparation/processing of HSC. Chapters 2 and 3 address: the preparation of HSC, adverse reactions and their causes and nursing care before, during and after the infusion of HSCs; all of them, according to each modality, Chapter 2 for fresh cells with 38 care and Chapter 3 for cryopreserved-thawed cells with 37 care. The chapters are presented in the form of text, figures, charts and flowcharts. In addition to these chapters the protocol has references and attachments.

In this manuscript it was chosen the approach of nursing care during infusion of HSC in both modalities, as shown in Charts 3 and 4. For the fresh infusion mode, with bone marrow and peripheral blood sources and for cryopreserved-thawed infusion, the bone marrow, peripheral blood and blood sources in the placental umbilical cord.

**Chart 3 - Nursing care during the infusion of fresh hematopoietic stem cells.**  
Curitiba, PR, Brazil, 2016

Nº	Nursing Care
1	Initiate infusion of HSC immediately, when the following situations are satisfactory: - HSC bag(s) released by the Laboratory of Cellular Manipulation and Cryobiology; - Patient able to start the infusion.
2	Conduct a double checking (with a member of the nursing team) on the identification of the HSC bag with the Infusion Report from the Laboratory of Cellular Handling and Cryobiology. In ABO Incompatibility greater or bi-directional check the final volume of red blood cells.
3	Perform double checking, when entering the patient's room, with the full name on the identification bracelet and/or confirmed by the patient.
4	Check vital signs: immediately before starting infusion.
5	Keep the patient monitored (pulse oximetry) in the first hour of infusion. Monitoring should be maintained when adverse reactions occur.
6	Stay in the patient's room for the first hour of HSC infusion.
7	Stay on duty at bedside. Keep the remaining HSC bags (if there are more than one) properly identified in cooler at the Nursing Station and reinforce this information in the shift change.
8	Infuse HSC into blood transfusion set. Never use a transfusion set with a leukoreduction filter. In case there is more than one bone marrow bag, change the transfusion set each time you change the bag.
9	Infuse HSC in the most calibrated CVC pathway, after performing flushing in CVC with a syringe containing 0.9% saline solution.
10	Maintain intravenous hydration of the patient according to medical prescription.
11	Check vital signs: - every 15 minutes in the first hour of infusion; - every 30 minutes in the second hour of infusion; - every hour in the subsequent hours*. *The increase in the time interval should also follow the clinical status of the patient: if necessary, the vital signs should be checked more frequently.
12	Homogenize the CTH bag and check the drip speed during the infusion, every 01 hour.
13	Monitor the volume and appearance of the patient's diuresis and monitor fluid balance.
14	Program the infusion of the HSCs with the flow rate of 3ml/kg/h for cases of ABO compatibility or minor ABO incompatibility between donor and recipient.
15	Schedule the infusion of HSCs with the initial flow rate of 1ml/kg/h, which should be increased to 2ml/kg/h in the next half hour, and to 3ml/kg/h in the subsequent half hour, in cases of higher ABO incompatibility or bi-directional, between donor and recipient.
16	Decrease the speed or temporarily interrupt the infusion (depending on the severity of the reactions) if the patient experiences adverse reactions during the infusion of HSCs. Report responsible physician and perform according prescribed by him.

HSC = hematopoietic stem cells; CVC = central venous catheter.

**Chart 4 - Nursing care during infusion of cryopreserved-thawed hematopoietic stem cells.**  
Curitiba, PR, Brazil, 2016

Nº	Nursing Care
1	Start infusion of HSC immediately after thawing.
2	Conduct a double checking (with a member of the nursing team or with biochemistry) on the identification of the HSC bag with the Infusion Report from the Laboratory of Cellular Manipulation and Cryobiology.
3	Perform double checking, when entering the patient's room, with the full name on the identification bracelet and/or confirmed by the patient.
4	Guide the patient that he can suck candy* during and after the infusion of HSCs. *Candy previously released by the Nutrition Service and/or doctor.
5	Check VS immediately before starting infusion.
6	Maintain the patient monitored (pulse oximetry and cardiac monitoring) during the infusion of HSCs.
7	Stay in the patient's room throughout the infusion of HSC.
8	Infuse HSC into blood transfusion equipment via gravitational*. Never use equipment with a leukoreduction filter. *In cases of difficult gravitational flow, the infusion can be done using a 60 ml syringe and a three-way device. This is connected between the transfusion set and the CVC. The contents of the bag are aspirated with the syringe and it is injected by the CVC with the syringe.
9	Infuse HSC in the most calibrated CVC pathway, after performing <i>flushing</i> in CVC with a syringe containing 0.9% saline solution.
10	Maintain in the other CVC path only intravenous hydration, according to medical prescription.
11	Check vital signs every 15 minutes (remembering that the patient should have continuous pulse oximetry and cardiac monitoring).
12	Notify the biochemistry for the thawing of the next bags, in the cases of thawing at the bedside.
13	Monitor the volume and appearance of the patient's diuresis and monitor fluid balance.
14	Program the infusion of each bag (it can be one or more bags) at a speed of 10ml/minute, regardless of the way of thawing (bedside, dilution or washing). Start the infusion slowly and schedule the end to the calculated time* if the patient tolerates well. *This infusion time should also be respected in cases of use of syringe and three-way device.
15	Decrease the speed or temporarily interrupt the infusion (depending on the severity of the reactions) if the patient experiences adverse reactions. Report responsible physician and perform according prescribed by him. Infuse each bag within 30 minutes in case of reaction.

HSC = hematopoietic stem cells; CVC = central venous catheter.

## DISCUSSION

The nursing care protocol on day zero of the HSCT characterized, in the Convergent Care Research, the contribution to the development of knowledge that mobilize the improvement of the practices of assistance in the research area.<sup>13</sup> It was an instrument that defined the interventions of good practice for safe nursing care and quality to be provided to STMO.

The step covered in this manuscript, care during the infusion of HSC, consisted of 16 care for the fresh modality and 15 for cryopreserved-thawed, some of which are similar.

The first caution for both modalities refers to the immediate beginning of the infusion of the HSCs. In fresh mode, this care is based on the maximum allowable interval of 48 hours between completion of collection of donor HSCs and their fresh infusion at the recipient.<sup>2,17</sup> Therefore, it should be noted that in cases of bone marrow or peripheral blood HSC from another national or international service, for use in unrelated allogeneic transplants, special attention should be paid due to the time spent in the transport of these cells. In the cryopreserved mode, the infusion of the HSCs should be immediately after thawing. For cryopreservation of the cells a cryoprotectant compound called Dimethyl sulfoxide (DMSO) is used. After thawing, the previously cryoprotective compound becomes toxic to the HSCs.<sup>2,18-19</sup>

However, before initiating the infusion of HSCs, the nurse must perform a double check of the identification of the HSC bag, with another professional, and double conference with the patient, for both modalities. As established by Ordinance No. 158 of 2016, which redefines the technical regulation of hemotherapy procedures, the receipt and checking of the identification data of products derived from the blood and recipient are the responsibility of the nurse.<sup>20</sup> According to recommendations of FACT and the American Association of Blood Banks (AABB), the patient and product data to be infused should be checked, such as patient identification and registration, product name and date/time of collection and preparation, product volume, if any processing was performed and which, ABO and Rh typing.<sup>2,10,21</sup>

In addition to the checking data, the nurse should be aware of the amount of DMSO that will be infused into the patient in cryopreserved mode and the residual volume of red blood cells in greater and bidirectional ABO incompatibility in fresh mode.<sup>10</sup> The concentration of DMSO presented in the literature ranges from 5 to 10%, the latter being the most common.<sup>2,18,22</sup> Considering the concentration of 10%, the patient can receive a maximum of 1ml/kg/day of DMSO, remembering that if so, each 100 ml of cryopreserved product will contain 10ml of DMSO.<sup>2,21</sup>

For the fresh mode, the nurse's attention turns to the residual volume of red cells in cases of greater or two-way ABO incompatibility. In these incompatibilities the plasma of the receptor has antibodies against the red blood cells of the donor, being necessary the procedure of removing red blood cells. The aim is to reduce red cells to a minimum to reduce the occurrence and severity of acute hemolysis.<sup>23-24</sup> FACT recommends that services define the red blood cell removal procedure and the maximum residual volume of red cells for these cases, but does not address what this value is.<sup>10</sup> A Canadian study aimed at determining the volume of red blood cells that can safely be infused in children in allogeneic transplantation using fresh bone marrow presented an average of 0.33ml/kg of infused red blood cells, ranging from 0.04 to 3.16ml/kg.<sup>25</sup> Another study found that the volumes between 20 and 30ml for adults and between 0.2 and 0.4ml/kg for children were safe.<sup>24</sup>

Caution addressed for the cryopreserved modality was to guide the patient to suck candy during and after the infusion of HSCs. After thawing, substances resulting from the metabolism of DMSO are excreted via the renal, pulmonary and dermatological routes, resulting in the exhalation of an odor and breath similar to corn or garlic cream, which are the major responsible for the occurrence of nausea and emesis.<sup>19,26-27</sup> In the national study that resulted in a video showing cryopreserved-thawed CTH infusion, patients were offered candy to suckle during and after infusion.<sup>28</sup> For the same purpose, to ease the discomfort of patients and to decrease the occurrence of these adverse reactions, a randomized American study examined the feasibility and efficacy of using orange wedges in three groups of patients. The first group ate orange; the second made aromatherapy with the same fruit; and the third control group. The conclusion was the efficacy of ingestion of orange wedges to treat symptoms associated with DMSO toxicity.<sup>29</sup> Another randomized study carried out in Turkey aimed to

explore the effect of strawberry-flavored lollipops and concluded that this measure has a promising effect in reducing nausea and emesis and is easy to administer and low cost.<sup>30</sup>

Nursing care aimed at the immediate identification of adverse reactions, allowing early intervention, are the vital signs gauging, patient monitoring and nurse's stay next to the patient. The measurement of vital signs immediately before the start of the infusion of HSC aims to establish normal parameters to facilitate the detection of changes that may occur during infusion and early intervention. It is foreseen in Resolution RDC No. 56 of 2016 and in recommendation of AABB, that the patient must have their vital signs checked before the beginning of the infusional act.<sup>10,20</sup> During the infusion of HSCs it is recommended to be frequent at intervals of 10 to 15 minutes.<sup>2,31</sup> On maintaining the measurement of vital signs/monitoring after the infusion is recommended, due to the occurrence of adverse reactions in this period.<sup>21</sup> An American study that aimed to indicate which characteristics of the patient and the infusion are associated with the occurrence of adverse reactions, maintained the measurement of vital signs/monitoring up to one hour after the end of the infusion.<sup>31</sup> Other authors report the occurrence of reactions up to six hours after the end, especially those related to the cardiovascular system, which shows the importance of maintaining this care.<sup>2</sup>

Studies on adverse reactions related to HSC infusion have shown that those associated with the respiratory and cardiovascular systems, detectable by vital signs/patient monitoring, are the most frequent being bradycardia, tachycardia, hypotension, precordial pain, throat irritation, cough.<sup>22</sup> In an American study these reactions were also frequent, besides others such as fever, hypothermia, headache and back pain, also detectable by the measurement of the vital signs.<sup>31</sup>

In the nursing care protocol, the frequency of vital signs measurement and patient monitoring were established, however, the interval could be altered by the nurse, as assessed by the clinical condition of each patient. Both care are more frequent in cryopreserved-thawed mode, which is due to the higher incidence of complications related to this mode.<sup>26-27,31</sup>

For both infusion modes, HSCs should be infused gravitationally by central venous catheter, in blood transfusion equipment, after performing flushing with 0.9% physiological solution. The choice for the central route ensures the infusion of cells in the circulatory system and prevents damage to the peripheral venous network, since cryopreserved products have high osmolarity due to the presence of DMSO. In addition, a calibrated central pathway will ensure infusion of the product at the correct time, which is short when HSCs are cryopreserved-thawed.<sup>2,21</sup> The central pathway is also the option for infusion of fresh HSC, as well as ensuring the infusion of cells into the circulatory system, is ideal for infusion of large volumes, as can occur when the source is bone marrow.<sup>2,21</sup> The physiological 0.9% solution is the only one that does not cause damage to HSCs or blood products. The *flushing* with this solution prior to the initiation of the infusion of the HSCs prevents damage to these cells, upon contact with other fluids or medications.<sup>2,20-21</sup>

The blood component transfusion equipment has the function of reducing the risk of administration of clots and aggregated cellular components.<sup>2,21</sup> This care is also described in Ordinance No. 158 of 2016, which states that the infusion of blood products must be made by means of pyrogen-free and disposable equipment, with a filter that will retain clots and aggregates alternatively.<sup>10</sup> It was defined by the group of nurses that the equipment will be changed when there are two or three bags of fresh HSC, but will not need to be exchanged between bags of cryopreserved-thawed HSC, provided there is no contamination or saturation thereof.

It was also defined that the infusion of cryopreserved-thawed HSC can be done by manual technique with syringe, if the HSCs do not infuse gravitationally in the recommended time. This option must be used to comply with the maximum time limit of 30 minutes for infusion of HSCs after thawing.<sup>2,18</sup> For this technique, a three-way device is connected between the equipment and the CVC. With a 60 ml syringe the contents of the bag are aspirated and injected manually by the CVC.

An American study aimed at determining the effect of two infusion techniques on the occurrence of adverse reactions concluded that gravitational infusion protects patients from the occurrence and severity of complications.<sup>19</sup> Therefore, it was defined in the protocol by the gravitational infusion. The manual technique will only be used in specific situations of difficulty of gravitational infusion.

The care of the maintenance of intravenous hydration, monitoring of the volume and aspect of diuresis and monitoring of the fluid balance are care that apply to both infusion modalities. Aim to prevent adverse reactions, especially hemolysis; besides the immediate identification of hemoglobinuria in cases of acute hemolysis, which provides early intervention.

The maintenance of intravenous hydration aims to minimize the side effects and toxins associated with the infusion of the HSCs. This care should be started six hours before the infusion and be maintained until two hours after.<sup>2</sup> The explanation is that hydration has the effect of alkalinizing urine, and thereby decreases the renal toxicity associated with hemoglobinuria, common adverse reaction in the infusion of cryopreserved-thawed HSC (hemolysis due to cryopreservation and thawing) and fresh HSC (hemolysis due to ABO incompatibility between donor and recipient).<sup>2,23</sup> Intravenous hydration is essential in HSCT with greater or bi-directional ABO incompatibility to attenuate the consequences of the acute hemolytic reaction.<sup>24</sup> In an American study, the 645 patients who composed the sample were submitted to cryopreserved-thawed HSC infusion, received intravenous hydration of 5% glucose solution and 0.9% physiological solution. In this study, hemoglobinuria occurred in 15 (2.33%) patients, demonstrating the importance of hydration.<sup>19</sup> In a Canadian study, 78 patients underwent fresh HSC infusion with greater or two-way ABO mismatch. They received intravenous hydration with the same solutions, which started 2 hours before and remained until 4 hours after infusion of the cells. Also in this study, in cases of hemoglobinuria, hydration was maintained until the urine staining normalized.<sup>25</sup>

Serious complications may occur such as acute renal failure and disseminated intravascular coagulation associated with hemolysis.<sup>2</sup> Monitoring the volume and aspect of diuresis/fluid balance of the patient facilitates the early detection of hemoglobinuria. These precautions, combined with the administration of intravenous hydration, can prevent the onset or worsening of a renal injury. Australian observational study presented as a result the absence of acute hemolysis in transplants with major or bi-directional incompatibility that used as source the fresh peripheral blood.<sup>32</sup> Comparing this finding, in an American study of 78 transplants with the same incompatibilities, with a fresh bone marrow source, 30 patients presented mild hemolytic reactions and five adverse reactions classified as clinically significant.<sup>25</sup> It is believed that this discrepancy is related to the fact that the peripheral blood has reduced red blood volume when compared to the bone marrow.

In order to prevent the occurrence of adverse reactions related to the infusion of large volumes, and also having as concern the maintenance of the viability of the HSCs, different infusion rates were determined. The speed/time of infusion of the HSCs varies according to the modality.

It was defined for the modality cryopreserved-thawed speed of 10 ml/minute, starting out slowly. Thus, a bag containing 100ml of product will be infused in approximately ten minutes. Some authors do not determine the speed, they only address that the cells must be infused slowly.<sup>28</sup> Others recommend infusion slowly started (2 to 4ml/minute), so the nurse can monitor adverse reactions. If well tolerated, it should be infused between 5 and 20ml/min.<sup>2,21</sup> And others recommend the exact speed of 10ml/min.<sup>6,19</sup> It is emphasized that the recommended speed must be maintained, regardless of the infusion mode (gravitational or manual technique).<sup>19</sup> The nurse, who will remain beside the patient during the infusion, should assess the occurrence and severity of adverse reactions. According to this assessment, if necessary, slow down or temporarily interrupt the infusion of HSCs and report to the physician for the necessary conducts. For cases of need for slower infusion speed or temporary interruption, it was determined that each bag could be infused up to 30 minutes, corroborating with the literature, so that there is no impairment of cellular viability.<sup>2,18</sup> A national study that aimed to identify

nurses' care on day zero demonstrated that the time of infusion of HSC in this modality ranged from 12 to 30 minutes.<sup>7</sup>

To the fresh mode, either bone marrow or peripheral blood HSC, some authors consider as an infusion time an average of 4 hours.<sup>2</sup> Others recommend the controlled speed, based on the characteristics of the product (source of HSC, presence of ABO incompatibility) allied to the clinical conditions of the patient.<sup>5</sup>

During the construction of the protocol, it was searched literature that based the time of infusion according to variables such as product volume and patient weight. An American study was found that reports infusion time varying according to volume, patient weight and residual volume of incompatible red blood cells, however, no calculation is given for infusion speed. In this study the mean infusion time was 4.5 hours (0.5-24 hours).<sup>25</sup> This same study suggests that, despite the severity of adverse reactions, bone marrow HSC can be infused at intervals of four to eight hours.<sup>25</sup> A national study aimed at identifying the adverse reactions that may occur during the infusion of HSCs and the nursing care associated with the procedure, treated as 3 to 6 ml/kg/h the infusion speed of blood products, being 1 ml/kg/h in more susceptible individuals.<sup>6</sup> A national study that observed the infusion of fresh HSC in the various types of ABO compatibility/incompatibility pointed out that the time ranged from 03:50 to 09:44.<sup>7</sup>

Therefore, based on scientific evidence, coupled with the experience of participating nurses and the confirmation that infusions with major and bidirectional incompatibility are more prone to complications, the flow rate of 3ml/kg/h for infusion of fresh HSC with lower ABO compatibility or incompatibility was defined. For greater or bi-directional ABO incompatibility between donor and recipient the initial flow rate was defined as 1ml/kg/h, progressing to 2ml/kg/h and then to 3ml/kg/h. As in cryopreserved mode, the infusion should have the flow decreased or temporarily discontinued despite the severity of adverse reactions.

Also in the fresh mode, during the infusion, the nurse should pay attention to the homogenization of the HSC bag, a care that avoids the accumulation of clots and aggregates in the transfusion set, which avoids the saturation of the same.<sup>2,21</sup>

The accomplishment of this research followed what is recommended by the Convergent Care Research methodology. According to it, besides other considerations, the research must be based on reliable sources of knowledge.<sup>13</sup> However, this was one of the fragilities found: the scarcity of nursing studies related to the issue of nurse's care on day zero of HSCT, which shows a gap and the need for further research in this area.

## CONCLUSION

This research was carried out following the methodological steps of the Convergent Care Research. The elaboration of the care protocol in the research stage was performed as recommended by the literature, since it used not only scientific evidence data, but also considered the experience of nurses and was built for the reality of the service. The participation of nurses in the protocol refinement and approval of it was fundamental and facilitated the subsequent use of this instrument.

The use of the Convergent Care Research methodology was a facilitator, since it provided the union of care practice with scientific research. The use of this methodology presupposes the participation of those involved in the care practice.

The protocol is composed of objective care, however the use of this instrument does not prevent or limit the nurses' safe, differentiated, individualized and humanized work process, which has its practice characterized by the union of the objective and subjective dimensions of care.

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## NOTES

### CONTRIBUTION OF AUTHORITY

Study design: Figueiredo TWB, Mercês NNA.

Data collect: Figueiredo TWB, Silva LAA, Machado CAM.

Data analysis and interpretation: Figueiredo TWB, Silva LAA, Machado CAM.

Discussion of the results: Figueiredo TWB, Mercês NNA.

Writing and / or critical review of content: Figueiredo TWB.

Review and final approval of the final version: Mercês NNA.

### ETHICS COMMITTEE IN RESEARCH

Approved by the Ethics Committee in Research with Human Beings of the *Hospital de Clínicas, Universidade Federal do Paraná*, under Opinions n.1,537,465 and n.1,607,139 (amendment of the project) and Certificate of Presentation for Ethical Appreciation (CAAE) 55116016.5.0000.0096.

### CONFLICT OF INTEREST

There is no conflict of interest

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