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Adverse reactions on day zero of hematopoietic stem cell transplantation: integrative review

Reações adversas no dia zero do transplante de células-tronco hematopoéticas: revisão integrativa

Reacciones adversas en el día cero del trasplante de células madre hematopoyéticas: revisión integradora

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ABSTRACT

Objective: To identify the adverse reactions associated with the infusion of hematopoietic stem cells on day zero of hematopoietic stem cell transplantation.

Methodology: Integrative literature review, without temporal cut, with search in the following databases: PubMed, CINAHL, SCOPUS, BVS, SciELO, Web of Science and CAPES; the final sample consisted of 18 scientific articles, published between 1998 and 2017, based on the inclusion and exclusion criteria.

Results: Mild and moderate adverse reactions were the most frequent in studies that used the classification by severity, and nausea and emesis had the highest incidence; the most affected organ systems were the cardiovascular, respiratory and gastrointestinal.

Conclusion: The main adverse reactions identified in the studies were nausea and emesis. Those classified as mild and moderate were the most frequent in the studies that used the severity classification; and the cardiovascular, respiratory and gastrointestinal systems were the most affected in those that used the classification by organic systems.

Keywords: Hematopoietic stem cell transplantation. Hematopoietic stem cells. Nursing. Review.

RESUMO

Objetivo: Identificar as reações adversas ligadas à infusão de células-tronco hematopoéticas no dia zero do transplante de células-tronco hematopoéticas.

Método: Revisão integrativa da literatura, sem recorte temporal, a partir de fontes de informação: PubMed, CINAHL, SCOPUS, BVS, SciELO, Web of Science e CAPES; a amostra final foi constituída por dezoito artigos científicos, publicados entre 1998 e 2017, com base nos critérios de inclusão e exclusão.

Resultados: Reações adversas leves e moderadas foram mais frequentes nos estudos que utilizaram a classificação por severidade, sendo náusea e êmese as de maior incidência; os sistemas orgânicos mais afetados foram o cardiovascular, respiratório e gastrointestinal.

Conclusões: As principais reações adversas identificadas nos estudos foram náusea e êmese. As classificadas como leves e moderadas foram as mais frequentes nos estudos que utilizaram a classificação por severidade; e os sistemas cardiovascular, respiratório e gastrointestinal foram os mais afetados naqueles que utilizaram a classificação por sistemas orgânicos.

Palavras-chave: Transplante de células-tronco hematopoéticas. Células-tronco hematopoéticas. Enfermagem. Revisão.

RESUMEN

Objetivo: Identificar las reacciones adversas ligadas a la infusión de células madre hematopoyéticas en el día cero del trasplante de células madre hematopoyéticas.

Metodología: Revisión integrativa de la literatura, sin recorte temporal, a partir de los siguientes bancos de datos: PubMed, CINAHL, SCOPUS, BVS, SciELO, Web of Science y CAPES; la muestra final fue constituida por 18 artículos científicos, publicados entre 1998 y 2017, sobre la base de los criterios de inclusión y exclusión.

Resultados: Las reacciones adversas leves y moderadas fueron las más frecuentes en los estudios que utilizaron la clasificación por severidad, siendo náuseas y vómito las de mayor incidencia; los sistemas orgánicos más afectados fueron el cardiovascular, respiratorio y gastrointestinal.

Conclusión: Las principales reacciones adversas identificadas en los estudios fueron náuseas y éstas. Las clasificadas como leves y moderadas fueron las más frecuentes en los estudios que utilizaron la clasificación por severidad; y los sistemas cardiovascular, respiratorio y gastrointestinal fueron los más afectados en aquellos que utilizaron la clasificación por sistemas orgánicos.

Palabras clave: Trasplante de células madre hematopoyéticas. Células madre hematopoyéticas. Enfermería. Revisión.

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INTRODUCTION

The hematopoietic stem cell transplantation (HSCT) is a treatment involving the submission of the patient to chemotherapy and/or radiotherapy, followed by the infusion of progenitor cells or hematopoietic stem cells (HSC). Currently, it is a therapy applied with the objective of obtaining a long remission or the cure of patients affected by malignant or non-malignant disorders of the hematopoietic system[1-2]. It is categorized regarding the allogeneic donor, when the patient receives the HSC from another person, a relative or not; eautogenic, when it uses the patient's own previously collected cells[1].

The HSCT is divided into three phases: pre, trans and post-transplantation. The infusion of the HSC occurs in the trans phase, called day zero[1-2]. The cells can be obtained from the bone marrow (BM), peripheral blood (PB) after mobilization with chemotherapy and/or growth factors and placental umbilical cord blood (PUCB)[2-3]; and constitute the product to be infused into the patient on day zero. These cells can be collected and infused freshly in patients undergoing allogeneic transplants; or cryopreserved for later use, such as in autogenic and PUCB cell transplantation[4-5]. In the cryopreservation process, the Dimethyl Sulfoxide (DMSO) is used with the function of protecting the cells, maintaining its viability[4].

The literature does not specify which professional performs the HSC infusion[6], although in Brazil the nurse is the one who is legally qualified for this job, according to the Resolution of the Federal Nursing Council (COFEN – "Conselho Federal de Enfermagem", in Portuguese) No. 200/1997, which deals with the competencies of the nurse in the HSCT and the execution of procedures related to the aspiration and infusion of HSC[7]. The nurses' work regarding the HSC infusion is corroborated by national studies[8-10].

On Day Zero, the nurse is responsible for several patient care activities before, during and after the HSC infusion. In addition, they should guide the patient and their relatives about the care and possible complications expected for this day[6,8]. The action of infusing HSC is considered a specialized nursing care of the nurse[11] and he/she must be prepared to perform it, in addition to preventing, identifying and intervening in possible complications or complications related to the procedure[8,11].

The HSC are infused on Day Zero, fresh or cryopreserved, after thawing. In the literature, infusion-related adverse reactions are described as mild or severe[3], or receive classification by degree of severity: mild (1), moderate (2), severe (3), disabling or life-threatening adverse reaction (4) and death due to the adverse reaction (5)[5,12]. They can affect the cardiovascular, gastrointestinal, neurological, renal and respiratory systems[2,5,9,13], in addition to reactions classified as dermatological or allergic[2,5].

Adverse reactions that occur during or after the infusion of HSC are linked to the characteristics of the infused product as: volume, number of total nucleated cells and granulocytes, residual volume of plasma and/or red blood cells in cases of ABO incompatibility, toxicity of the DMSO preservative and product contamination. And also to the characteristics of the patient, such as sex, age, weight, disease and clinical condition[3,5,13-14].

Because of the inherent risk of complications related to HSC infusion, nurses should be aware of adverse reactions, in order to facilitate the introduction of preventive and corrective measures[8], being thus able to provide a safe and quality care to the patient.

Considering what has been said above, this article aims to: identify the adverse reactions associated with the HSC infusion on day zero of the HSCT.

METHODOLOGY

This is an integrative review of the literature. This method is able to summarize the literature to provide a more comprehensive understanding of a specific phenomenon; and thus, it has the potential to present the state of science and contribute to the development of theories[15].The synthesis of the completed research was developed based on the following steps[15]:

1) Formulation of the problem/question: "What adverse reactions have been reported in the literature related to infusion of hematopoietic stem cells on day zero of the hematopoietic stem cell transplantation?"

2) Data collection or definitions about the literature search: the search for the studies was performed electronically, with no temporal cut, in September and October of 2017, in the following databases: *National Library of Medicine* (PubMed), *The Cumulative Index to Nursing and Allied Health Literature* (CINAHL), SCOPUS, Virtual Health Library (BVS – "Biblioteca Virtual em Saúde", in Portuguese), *Scientific Electronic Library* (SciELO), Web of Science and Journal Platform of the Coordination of Improvement of Higher Education Personnel (CAPES – "Portal de Periódicos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior", in Portuguese). The following search strategy was used: *"Day zero"* OR *"Hematopoietic stem cell infusion"* OR *"Hematopoietic progenitor cell infusion"* AND *"Adverse reactions"* OR *"Adverse events"* OR *"Adverse effects"* OR *"Side effects"*. These descriptors are not standardized, according to the *Medical Subject Headings* (MeSH), however they were chosen be-

cause they enabled the finding of articles that answered the problem/research question. The use of standardized descriptors resulted in a wide search, however, with unsatisfactory results to answer the problem/research question. The following inclusion criteria were established: to be an original scientific article published in national and international literature that comprehended the theme, with texts available in full online, in journals indexed in the electronic information sources consulted, in the English, Portuguese or Spanish languages.

3) Evaluation of data: the titles and abstracts were read in order to select the studies that fit the objective of the review. Those that did not respond to the research problem, the review studies and the repeated ones were excluded. From this selection, the studies were read in full. For this, an instrument was prepared containing: title, authors, language, year of publication, location, objective, methodological design, participants, level of evidence, described adverse reactions and conclusions.

The evidence level was classified according to the categorization of the Agency for Health Care Research and Quality (AHRQ). The quality of the evidence is classified into seven levels: I – meta-analysis and systematic reviews; II – individual studies/experimental design; III – evidence of almost experimental study; IV – descriptive studies with a qualitative approach; V – case studies; VI – descriptive studies; VII – experts' opinion[16].

Steps 2 and 3 were independently performed by two reviewers. The selection process of the studies that composed the sample was based on the criteria of the Preferred Reporting Items for Systematic Review and the Meta-Analyzes (PRISMA)[17] as shown in Figure 1.

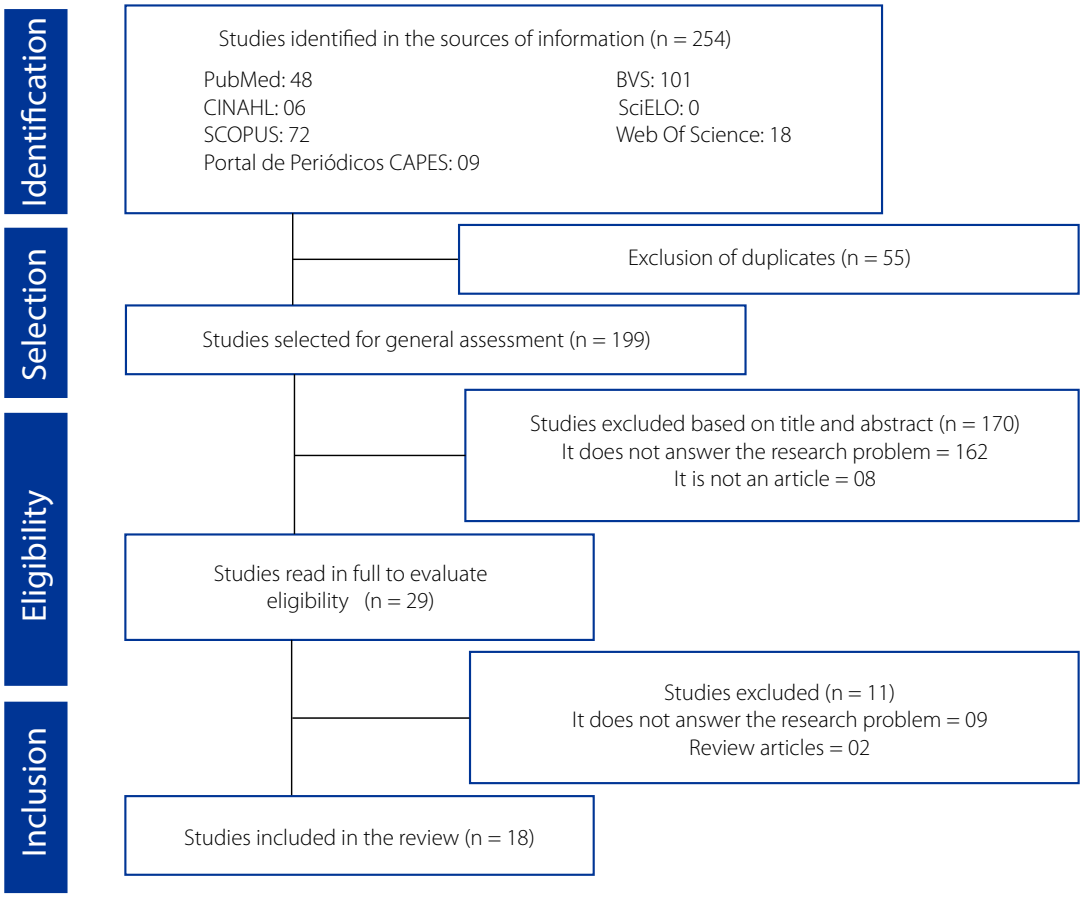

Figure 1 - Flow diagram for the selection of studies
Source: PRISMA[17]

4) Data analysis: performed by reading the studies in full and summarizing the content.

5) Presentation and interpretation of the results: the results were presented in the form of charts, showing the characterization of the studies and the main findings and conclusions.

RESULTS

The sample consisted of 18 studies (E_1 to E_{18}) published between 1998 and 2017 in the English language. The publications were from the United States (five studies), followed by Spain, Switzerland and Turkey with two studies each; Canada, Croatia, France, Italy, Japan, Norway and the United Kingdom, with one publication each.

All the studies were original, with ten prospective, four retrospective, two retrospective cohort comparisons with prospective studies; and two case reports. As for the level of evidence, four level II studies, three level IV, 11 level VI.

Chart 1 presents the characterization of the studies regarding the main author, year, country of publication, level of evidence, research objective and methodological design (type of study, participants). They are arranged in ascending order of year of publication.

Main author/Year/ Country/Level/No.	Characterization of the studies
Abdel-Razeq H[18] / 1998 / United States / II / E_1	**Objective:** To test the hypothesis that the infusion of HSCT on day 01 is well tolerated when compared to infusions in multiple days.
	Methodology: Prospective randomized study with 60 patients who underwent autologous HSCT using cryopreserved HSCPB. They were divided into: Group 1: infusion in 1 day; Group 2: infusion in 2 days; Group 3: infusion in 3 days.
Zenhäusern R[19]/ 2000 / Switzerland / VI / E_2	**Objective:** To describe the case report of a patient with primary amyloidosis who developed severe cardiac arrhythmia after the infusion of HSBC.
	Methodology: Case report of a patient who underwent autologous HSCT using cryopreserved HSCPB.
Perseghin P[20] / 2000 / Italy / VI /E_3	**Objective:** To investigate the incidence and severity of AR related to the infusion of HSC.
	Methodology: Retrospective study carried out with 30 patients (32 infusions) who underwent autologous HSCT using HSCBM (6 patients) and HSCPB (24 patients).
Calmels B[21] / 2007 / France /IV / E_4	**Objective:** To perform a systematic evaluation to find out factors associated with the occurrence of AR
	Methodology: Prospective cohort study with 460 patients (490 infusions) who underwent autologous HSCT, with cryopreserved HSCPB.
Konuma T[22] / 2008 / Japan / VI / E_5	**Objective:** To evaluate the incidence and significance of the toxicity related to the infusion of HSC.
	Methodology: Prospective study with 34 patients who underwent allogeneic HSCT, with cryopreserved HSCUPCB.
Ozdemir E[23] / 2008 / Turkey / II / E_6	**Objective:** To explore the effect of the strawberry-flavored lollipop on nausea and emesis related to cryopreserved HSC infusion.
	Methodology: Prospective randomized study with 158 patients who underwent autologous HSCT with cryopreserved HSCPB. They were divided into: Group 1: did not receive the strawberry lollipop. Group 2: received the strawberry lollipop immediately before and during the infusion of HSC.
Bojanic I[24] / 2008 / Croatia / VI / E_7	**Objective:** To evaluate the toxicity related to the autologous HSCPB infusion.
	Methodology: Prospective study with 215 patients (262 infusions) who underwent autologous HSCT with cryopreserved HSCPB.
Akkök CA[25] / 2009 / Norway / II / E_8	**Objective:** To investigate whether the depletion of DMSO by the manual washing technique reduces the frequency of AR
	Methodology: Prospective randomized study with 53 patients who underwent autologous HSCT using cryopreserved HSCPB. They were divided into: Group 1: received HSC without manipulation. Group 2: received manipulated HSC to reduce the amount of DMSO.

Martín-Henao[26] GA / 2010 / Spain / IV / E_9	**Objective:** To evaluate the incidence and severity of AR and to analyze the variables associated with the clinical toxicity during the infusion of cryopreserved HSCPB.
	Methodology: Prospective cohort study with 398 patients (423 infusions) who underwent autologous or allogenic HSCT, with cryopreserved HSCPB.
Sánchez-Salinas A[27] / 2012 / Spain / II / E_{10}	**Objective:** To test whether the depletion of DMSO by automated washing decreases AR in cryopreserved HSC infusion.
	Methodology: Retrospective cohort study with 26 patients (53 infusions) (HSC with DMSO depletion) compared to a prospective study with 26 patients (46 infusions) (HSC without DMSO depletion). Both groups performed autologous HSCT, with cryopreserved HSCPB.
Khera N[12] / 2012 / United States / IV / E_{11}	**Objective:** To evaluate the impact of changing the institutional policy on security related to the infusion of cryopreserved HSCPB.
	Methodology: Retrospective cohort study with 288 patients (325 infusions) compared to a prospective study with 479 patients (519 infusions) who underwent autologous HSCT using cryopreserved HSCPB. Compared the moments before and after the implementation of the policy of limiting the total daily dose of nucleated cells and/or granulocytes.
Holbro A[28] / 2014 / Switzerland / VI / E_{12}	**Objective:** To measure the changes in hemostasis during HSCT and to investigate the association of these changes with HSCT complications.
	Methodology: Prospective study with 54 patients who underwent autologous or allogenic HSCT, using cryopreserved HSCPB.
Mulay SB[29] / 2014 / United States / VI / E_{13}	**Objective:** To determine the effect of two infusion techniques (manual vs. syringe vs. gravitational) on the occurrence of AR related to the infusion of HSC and to determine the influence of other variables.
	Methodology: Retrospective study with 645 patients (688 infusions) who underwent autologous or allogenic HSCT with cryopreserved or fresh HSCPB.
Morris C[30] / 2014 / United Kingdom / VI / E_{14}	**Objective:** To examine the strategies employed by the European HSCT Group centers to reduce transplantation toxicity, in particular strategies to reduce the amount of DMSO and its impact on the patient.
	Methodology: A prospective study describing the use of DMSO in 64 centers of the European HSCT Group. 1,651 patients who underwent autologous HSCT with cryopreserved HSC (unspecified cell source) were analyzed.
Vidula N[5] / 2015 / United States / VI / E_{15}	**Objective:** To question which patient and infusion characteristics may be associated with AR and identify potentially modifiable factors to prevent them.
	Methodology: Retrospective study with 460 patients who underwent autologous or allogeneic HSCT using cryopreserved HSCPB.
Truong TH[31] / 2016 / Canada / VI / E_{16}	**Objective:** To determine the incidence and severity of AR occurring during the infusion of HSC in pediatric patients undergoing allogeneic and autologous transplantation and to examine the risk factors for the development of these reactions.
	Methodology: Retrospective study was with 213 patients (361 infusions) who underwent autologous or allogenic HSCT with HSCPB, HSCBM and HSCUPCB cryopreserved or fresh.
Otrock ZK[32] / 2017 / United States / VI / E_{17}	**Objective:** To evaluate the incidence and to analyze the factors that contribute to the occurrence of AR in the infusion of cryopreserved HSC in autologous HSCT.
	Methodology: A prospective study with 1191 patients (1269 infusions) who underwent autologous HSCT using cryopreserved HSCPB.
Ataseven E[33] / 2017 / Turkey / VI / E_{18}	**Objective:** To describe the case report of a patient who developed seizures after the infusion of cryopreserved HSC.
	Methodology: Case report of a patient who underwent allogeneic HSCT using fresh HSCBM (day zero) and cryopreserved HSCBM (on the following day).

Chart 1 - Characterization of the studies that composed the sample

Source: Research data, 2018.

HSCT: Hematopoietic stem cell transplantation; HSCPB: Hematopoietic stem cells from peripheral blood; HSCBM: hematopoietic stem cells from bone marrow; HSC: hematopoietic stem cells; AR: adverse reaction or adverse reactions; HSCUPCB: hematopoietic stem cells from umbilical and placental cord blood; DMSO: Dimethyl sulfoxide.

Chart 1 shows that in some studies there was a divergence between the number of participants and the number of hematopoietic stem cell infusions, the latter being higher. This is due to the fact that, in some studies, the infusion of HSC occurred within two to three days.

Chart 2 is a synthesis of the findings of the studies: the adverse reactions (AR) found and the main conclusions obtained. The term chosen for this review was adverse reactions (AR) despite the wide variety found in studies such as adverse reaction, adverse event, adverse effect and side effect. In this synthesis, the order number used in chart 1 was maintained.

Nº.	Synthesis
E_1 (18)	**AR:** Of the 60 patients, 13 (22%) had AR. Rash or flushing, nausea, bradycardia, chills, hypotension, volume overload.
	Conclusion: There is no clinical benefit in dividing the infusion over multiple days, as the toxicity was similar in the 03 patient groups. However, the authors point out that the infusion division avoids the administration of a high dose of DMSO per day.
E_2 (19)	**AR:** Severe fatal bradyarrhythmia.
	Conclusion: Age and multiple organ dysfunction contributed to the outcome. The DMSO and the HCS volume contributed to the AR. The authors point out that the removal of DMSO and cell debris by washing procedures may reduce the risk of AR related to the infusion.
E_3 (20)	**AR:** Of the 32 infusions, AR was observed in 15 (47%). Bradycardia, hemoglobinuria, headache, abdominal pain.
	Conclusion: The AR were not severe and most were observed in the HSCBM infusion. The administration of pre-medications and the limitation of the amount of infused DMSO decrease the intercurrences during the infusion of the HSC.
E_4 (21)	**AR:** Of the 490 infusions, AR was observed in 66 (13%). Classified by degree of severity: Degree 1: throat irritation, excitement, visual impairment, nausea, pruritus, vertigo, chest pain. Degree 2: emesis, vasovagal episode, flushing, tremor, confusion, abdominal pain, headache. Degree 3: loss of sight. Degree 4: cardiac arrest, loss of consciousness, seizure.
	Conclusion: The occurrence of AR is directly related to the amount of granulocytes and not only to the toxicity of the DMSO.
E_5 (22)	**AR:** Of the 34 patients, 27 (80%) had AR and were classified as: Cardiovascular toxicity: diastolic hypertension, systolic hypertension, bradycardia and extra-systole. Non-cardiovascular toxicity: nausea, emesis, headache, chest discomfort and saturation drop.
	Conclusion: Cardiovascular toxicity with hypertension and bradycardia are more frequent AR in the cryopreserved HSCUPCB infusion. The results suggest that the infusion without manipulation after thawing is safe and well tolerated.
E_6 (23)	**AR:** Study with 158 patients that does not indicate the proportion of AR. In addition to nausea and emesis, focus of the study, other ARs were observed: hypoxia, cough, dyspnea, abdominal pain, tachycardia, agitation, chills, chest pain, fever, hypertension, hypotension, throat irritation, hiccups and arrhythmia.
	Conclusion: Cryopreserved HSC infusion can trigger nausea and emesis, probably because of the taste and flavor of the DMSO metabolites. The use of strawberry-flavored lollipops during the infusion of cryopreserved HSCPB in the autologous transplantation may be promising in reducing nausea and emesis, with ease of use and low cost.
E_7 (24)	**AR:** Of the 262 infusions, AR was observed in 149 (57%). Classified by degree of severity. Degree 1: hypertension, nausea, throat irritation, bad taste in the mouth, hot flashes, chills, abdominal pain, chest discomfort, dyspnea, palpitation and cough; Degree 2: emesis, hypertension with emesis, hypertension with nausea, hypotension with emesis, nausea with vertigo, hypertension with headache and nausea with palpitations. No degree 3 and 4 AR were observed.
	Conclusion: The amount of DMSO infused, the product composition (number of granulocytes) as well as the patient's characteristics (gender, diagnosis) are important factors for infusion-related toxicity.

E_{8} (25)	**AR:** Of the 53 patients, 19 (36%) had AR. Classified by organic systems: Cardiovascular: bradycardia, tachycardia, hypotension and hypertension. Gastrointestinal: nausea, emesis and abdominal pain. Other ARs: chest pain, headache and vasovagal episode.
	Conclusion: DMSO depletion by manual washing technique reduces AR related to the cryopreserved HSC infusion.
E_{9} (26)	**AR:** Of the 423 infusions, AR was observed in 105 (25%). Classified by organic systems. Gastrointestinal: nausea, emesis, diarrhea and abdominal pain. Respiratory: cough, throat irritation and dyspnea. Cardiovascular: hypertension, hypotension and chest pain. Dermatological: pruritus and erythema. Other ARs: hemoglobinuria, fever, arm pain and vasovagal episode. Neurological: headache, convulsion and loss of consciousness.
	Conclusion: The incidence and severity of the AR during the infusion of the cryopreserved HSCPB are related to the amount of granulocytes present in the product.
E_{10} (27)	**AR:** Study with 52 patients (26 in each group) that did not indicate the proportion of AR. Group that received HSC with DMSO depletion: abdominal pain, nausea and emesis. Group that received HSC without DMSO depletion: arrhythmia, hypotension, hypertension, nausea, emesis, abdominal pain and hypoxia.
	Conclusion: The DMSO depletion by the automated washing technique significantly reduces AR during the cryopreserved CTH infusion.
E_{11} (12)	**AR:** Study with 479 patients that does not indicate the proportion of AR. Seizure and chest pain.
	Conclusion: Limiting the daily dose of total nucleated cells and/or granulocytes (dividing the infusion over multiple days) reduces severe AR.
E_{12} (28)	**AR:** Of the 54 patients, 10 (19%) had AR. Fever and hives.
	Conclusion: The infusion of HSC containing DMSO reversibly activated the coagulation. However, this finding is not associated with acute AR and does not influence the graft attachment.
E_{13} (29)	**AR:** Of the 645 patients, 325 (50%) had AR. Flushing, nausea, hypertension, diarrhea, hypotension, hypoxia, hemoglobinuria, anxiety, pain, bradycardia, dyspnea, chills, and hives.
	Conclusion: The occurrence of AR related to the infusion of HSC is common. The infusion by the manual technique with syringe is associated to the higher incidence of AR when compared to the gravitational infusion. And patients who received fresh HSC developed less flushing than those receiving cryopreserved HSC.
E_{14} (30)	**AR:** Of the 1651 patients, 862 (52%) had AR. Nausea, emesis, hypertension and hypotension. The study also reported AR less recurrent classified as: respiratory, cardiac, neurological, gastrointestinal and allergic, but did not specify which.
	Conclusion: The implementation of methods that reduce the concentration of DMSO in the cryopreservation of HSC and emphasize the attention to the dose of this preservative to reduce toxicity and morbidity in the procedure of HSCT.
E_{15} (5)	**AR:** Of the 460 patients, 261 (57%) had AR. Classified by organic systems: Cardiovascular: bradycardia, chest pain, elevation of troponin, hypertension, hypotension, tachycardia and cardiac arrest. Respiratory: dyspnea and hypoxia. Constitutional or non-specific: headache, sweating, back pain, fever, hypothermia, throat irritation, heat waves and flushing. Neurological and/or Psychiatric: cerebrovascular accident, changes in vision, anxiety, unconsciousness, peripheral neuropathy and vertigo. Gastrointestinal: abdominal pain, emesis and nausea. Genitourinary: hemoglobinuria.
	Conclusion: AR are common during the infusion of HSC, and they are generally not life threatening and mostly affect the cardiovascular and respiratory systems. It has been observed that AR are more common in recipients of the second autologous HSCT and in those receiving a higher volume of red blood cells in allogeneic HSCT.

E_{16} [31]	**AR:** Of the 213 patients, the AR were classified by moment of occurrence and degree of severity. Degree 1: 55% during infusion and 62% within 24 hours of the infusion; Degree 2: 10% before and 18% after; Degree 3: 4% before and 7% after. The AR were: nausea, emesis, cough, flushing, tachycardia, hypertension, fever, headache, chest pain, pain, chills, bradycardia, hypotension, allergic reaction, visual disturbance, diarrhea, difficulty breathing, loss of consciousness and hypoxia.
	Conclusion: Infusion of HSC in pediatrics is a safe procedure. The results suggest that, unlike the adult literature, there is no association between the DMSO, granulocyte concentration and the development of a severe AR. The study supports the use of manipulated products to reduce the risk of AR to the infusion.
E_{17} [32]	**AR:** Of the 1269 infusions, AR was observed in 480 (38%). Flushing, nausea, emesis, hypoxia, chest pain, difficulty breathing, bradycardia, hypertension, hypotension and tachycardia.
	Conclusion: The AR, although not severe, occurred in more than a third of the patients. Many of the AR can be attributed to the DMSO and this is reflected in the infusion volume. They suggest the implementation of DMSO reduction protocols prior to the infusion. In addition to the DMSO, other variables such as granulocyte count, sex and diagnosis are risk factors for the occurrence of AR.
E_{18} [33]	**AR:** In the infusion of fresh HSC: no AR. Cryopreserved HSC infusion: headache, hypertension, bradycardia, hypothermia and convulsion.
	Conclusion: The neurotoxicity caused by the DMSO, although rare, is a serious complication. Attention should be paid to patients receiving cryopreserved HSC.

Chart 2- Synthesis of the findings of the studies
Source: Research data, 2018.

It is observed, in chart 2, that the adverse reactions were presented in non-standardized studies: some classified by organic system or severity and others did not use any classification. They were described in occurrence descending order of frequency. Some studies did not indicate the proportion of AR by number of patients and/or infusions that composed the sample.

DISCUSSION

Of the 18 studies that composed the sample, two were of the case report type and 16 used other methodologies. The frequency of adverse reactions varied from 0% with the infusion of fresh bone marrow[33] to 80% with the infusion of umbilical cord blood and cryopreserved placental blood[22]. A study developed in Canada with pediatric patients receiving fresh BM showed a 45% frequency of AR that are related to the final volume of the product and the presence of incompatibility of the ABO system between donor and recipient[2,14]. For the cryopreserved modality, there is added toxicity related to the presence of the preservative Dimethyl sulfoxide[13,34], which makes the frequency and severity of the adverse reactions higher in this modality. A study developed in Brazil showed a frequency of 83.3% of AR during the infusion of cryopreserved HSC[9].

As for the source of the hematopoietic stem cells used, a study from the United Kingdom did not reveal which source was used in the HSCT[29]. In 13 studies, the source of the HSC was peripheral blood[5,12,18-19,21,23-29,32]. A Turkish study used only bone marrow[33]and another Japanese study only the umbilical cord and the placental blood[22]. Only in the Italian and Canadian studies more than one source were used: BMandPB[20] and the three sources[31].

The fact that the peripheral blood is the most used source may be related to the most frequent type of transplantation, the autogenic one. In this type of transplantation, the PB is the source of choice due to the advantages over other ones, such as, lower risk of contamination with tumor cells, faster graft attachment and lower recurrence of the baseline disease in relation to the BM[2]. In a study that aimed to identify the adverse reactions and the nursing care inherent in the procedure, of 114 autogenic transplantations, all of them used the peripheral blood as a source[8]. It is observed, in general, a greater use of the PB in the HSCT, that previously had as priority cell source the BM. In this same study, of the 52 allogeneic transplantations, the PB was used in 26[8].

In the study carried out in Italy, which used bone marrow and peripheral blood, AR were more frequent with BM[20], due to the higher volume of product and erythrocytes of this source when compared to PB[3]. The Canadian study that used the three sources did not present the relationship between frequency of adverse reactions and the source used[31], but it is believed that, within the same in-

fusion modality (cryopreserved), adverse reactions to bone marrow and placental umbilical cord blood are analogous, since these two sources have very similar compositions[3].

Studies carried out in Turkey[33], United States[29] and Canada[31] showed differences regarding the infusion modalities (fresh and cryopreserved). In the case report developed in Turkey, the patient received infusion of fresh bone marrow on the first day and cryopreserved BM on the second day. Adverse reactions were observed only in the cryopreserved one[33]. The retrospective study developed in the United States showed that the cryopreservation of hematopoietic stem cells was a risk factor for the occurrence of flushing[29]. The Canadian study did not point out differences in AR between the two modalities, however, the authors support the use of products with a lower DMSO concentration[31]. This factor reinforces the need for greater attention to patients receiving the cryopreserved HSC infusion[3,9,33-34].

Eleven of the 18 studies reported toxicity due to the Dimethyl sulfoxide preservative[18-20,23-25,27-28,30,32-33], and its relation with several adverse reactions. Some suggest limiting the daily infused dose of DMSO, which could be achieved with a lower concentration of this preservative in the freezing, or with an infusion division over multiple days[18,20,30].

The division of the HSC infusion in two or more days was observed in 10 of the 18 studies: the patients had the infusion in multiple days[12,18,20-21,24,26-27,29,31-32]. However, only one randomized study verified the relationship between the infusion on more than one day and the occurrence of AR. It was concluded that there is no clinical benefit in dividing it over several days, however, the authors pointed out that the administration avoids high-dose administration of the preservative per day[18].

Others suggest the implementation of measures to reduce the toxicity[19,25,27,32]. These measures consist of processing or manipulating the product after thawing and prior to the infusion; called dilution and washing. The dilution is to add a solution to the product after thawing, causing the Dimethyl sulfoxide concentration to become half of the original. The washing involves the removal of the DMSO and cell debris. Products that do not undergo these procedures are called unmanipulated or unprocessed[3-4]. A literature review article with the aim of presenting adverse reactions in post-HSCT with cryopreserved products, the role of DMSO in these reactions and the options for the removal of this preservative; indicated that the dilution and washing are effective in reducing the occurrence and severity of adverse reactions, since they decrease or eliminate the DMSO and cellular debris, factors related to the occurrence of AR[13].

In addition to DMSO, another factor targeted as an AR trigger was the concentration of the total nucleated cells and/or granulocytes in the product[12,21,24,26]. One of these studies pointed to the division of the infusion over multiple days as a relevant factor in the reduction of severe AR related to this cause[12].

Regarding the factors associated with the patient, they are also determinants for the occurrence and severity of AR[19,24,32]. Only one of the 18 studies reported the occurrence of death related to the infusion of HSC, but the authors concluded that factors such as age, diagnosis and clinical condition were determinants for this outcome[19].

Although the factors related to the infused product and the patient were presented in the studies, the DMSO-related toxicity was the most present trigger factor, with frequent adverse reactions such as nausea and emesis[5,18,21-27,29-32]. This happens because after the thawing and the infusion of cryopreserved HSC, the substances resulting from the metabolism of DMSO are excreted through renal, pulmonary and dermatological via, resulting in the exhalation of an odor and halitosis similar to corn cream or garlic, which induce the appearance of nausea and emesis[13,34].

In the prospective randomized study conducted in Turkey that aimed to explore the effect of the use of the strawberry-flavored lollipop on nausea and emesis related to the cryopreserved HSC infusion, concluded that this measure has a promising effect in the reduction of these AR, besides being easy to administer and having a low cost[23]. A similar study demonstrated the efficacy of orange juice intake in preventing or reducing the occurrence of nausea and emesis[35]. Another study carried out in Brazil, with collection and infusion of the cryopreserved HSC, also presented a similar intervention: to provide candies to the patient before and during the infusion to reduce the occurrence of nausea and emesis[10].

Regarding the classification of adverse reactions, 10 studies did not perform the classification[12,18-20,23,27-29,32-33]. Three classified the AR by degree of severity[21,24,31]. In these studies, degrees 1 and 2 AR (mild and moderate, respectively) were the most prevalent. And only one reported the occurrence of degree 4 AR (incapacitating or life-threatening), exemplified by cardiac arrest, loss of consciousness and seizure)[21]. This fact reinforces the observation of some authors that the AR related to the infusion of HSC is mostly mild and of short duration[9].

Five studies classified the AR by organic systems. According to the authors, the most affected systems are the cardiovascular, respiratory and gastrointestinal, with reactions such as bradycardia, tachycardia, hypotension and

hypertension, dyspnea, hypoxia, throat irritation, nausea, emesis and abdominal pain[5,22,25-26,30]. A similar result was found in a Brazilian study, which also pointed out these three systems as the ones most affected by AR[9].

None of the studies that composed the sample addressed subjects related to the nursing care on day zero, related to the prevention, identification and intervention against AR. Some mentioned activities such as: administration of pre-medications[18-20,22-24,26,29,32-33], monitoring of vital signs, patient monitoring[5,20-22,24,26,32]and administration of intravenous hydration[18,20,29,31], which are care performed by the nurse. This fact can be explained by the objective of the studies and because none of them had this professional as the first author, what exposes the scarcity of studies on this topic in nursing. It is imperative for the nurse to know the AR and the measures to prevent them, identify them and perform interventions, since the nurse is the professional responsible for the infusion of HSC and who remains with the patient before, during and after the procedure.

CONCLUSIONS

The main adverse reactions related to the HSC infusion, which occurs on day zero of HSCT, are nausea and emesis. The PB was the most used source of HSC and the adverse reactions were more frequent and severe in the cryopreserved mode due to the DMSO preservative, absent in fresh HSC.

The mild and moderate AR were the most frequent in the studies that used the classification of severity. Those that used the classification by organic systems pointed the cardiovascular, respiratory and gastrointestinal systems as the most affected by AR.

None of the studies pointed to nursing care on day zero on the aspects of preventing, identifying and intervening in the presence of adverse reactions.

The review presented some limiting factors: the variety of adverse reaction terms, such as adverse event, adverse effect and side effect, presented in the studies; the different classifications of AR (by organic system, by degree of severity) or the lack of a classification system; factors that made it difficult to present and discuss the results in a uniform way.

The relevance of this review is the synthesis of evidence regarding the occurrence and severity of AR related to the infusion of HSC. The nurse, as a qualified professional to perform the infusion of HSC, should know the AR and its probable causes, aiming at the implementation of care that provides the patient's with physical and emotional well-being.

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