Review Article

Neurotoxicity presented by patients undergoing hematopoietic stem cell transplantation: a scoping review

Neurotoxicidades apresentadas por pacientes submetidos ao transplante de células-tronco hematopoéticas: uma revisão de escopo

Neurotoxicidades en pacientes sometidos al trasplante de células madre hematopoyéticas: una revisión de alcance

Anália Andréia de Araújo Nascimento[1] https://orcid.org/0000-0001-7492-2735
Katiane Domingos Soares[1] https://orcid.org/0000-0003-2594-887X
Maria Clara Siqueira de Almeida[1] https://orcid.org/0000-0003-4880-5759
Jéssica Cristina Alves de Melo[1] https://orcid.org/0000-0001-5515-2181
Ana Clara Paiva de Almeida[1] https://orcid.org/0000-0003-3969-1868
Débora Valéria de Oliveira Torres[1] https://orcid.org/0000-0002-7382-5922
Isabelle Campos de Azevedo[1] https://orcid.org/0000-0001-5322-7987

How to cite:
Nascimento AA, Soares KD, Almeida MC, Melo JC, Almeida AC Torres DV, et al. Neurotoxicity presented by patients undergoing hematopoietic stem cell transplantation: a scoping review. Acta Paul Enferm. 2022;35:eAPE00567.

DOI
http://dx.doi.org/10.37689/acta-ape/2022AR0005677

Keywords
Neurotoxicity syndromes; Hematopoietic stem cell transplantation; Bone marrow transplantation

Descritores
Síndromes neurotóxicas; Transplante de células-tronco hematopoéticas; Transplante de medula óssea

Descriptores
Síndromes de neurotoxicidad; Trasplante de células madre hematopoyéticas; Trasplante de médula ósea

Submitted
March 6, 2021

Accepted
April 28, 2022

Corresponding author
Anália Andréia de Araújo Nascimento
E-mail: analia.andreia.aa@gmail.com

Associate Editor (Peer review process):
Bartira de Aguiar Roza
(https://orcid.org/0000-0002-6445-6846)
Escola Paulista de Enfermagem, Universidade Federal de São Paulo, SP, Brazil

Abstract

Objective: To map the types of neurotoxicity presented by patients undergoing Hematopoietic Stem Cell Transplantation.

Methods: This is a scoping review, guided by the method proposed by the Joanna Briggs Institute, and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews recommendations. The search for studies was carried out between the months of July and August 2020 and took place in databases and in national and international theses and dissertations portals.

Results: The final sample consisted of 71 scientific articles, all in English. There was a highlight for the year 2018 with 14 (19%) publications. There was a prevalence of studies carried out in the United States of America with 29 (40.8%). Regarding the population, all (100%) articles are about patients undergoing hematopoietic stem cell transplantation who presented neurotoxicity. Regarding the chemotherapeutic agents used in the pre-transplantation regimen of hematopoietic stem cells, seven (9.8%) used the combination of Fludarabine and Cyclophosphamide, followed by Cyclosporine and Tacrolimus in six (8.4%), Cyclosporine in four (5.6%), Fludarabine in three (4.2%). As for the neurotoxicity presented in patients undergoing transplantation, the posterior reversible encephalopathy syndrome was evidenced in 19 (26.7%) studies. It should be noted that other studies have identified this syndrome, but have reported different symptoms.

Conclusion: The neurotoxicity presented by patients undergoing hematopoietic stem cell transplantation are posterior reversible encephalopathy, posterior reversible leukoencephalopathy, Wernicke's encephalopathy, hypertensive encephalopathy, metabolic encephalopathy, limbic encephalopathy, hemorrhagic complications and seizures.

Resumo

Objetivo: Mapear os tipos de neurotoxicidades apresentadas por pacientes submetidos ao Transplante de Células-Tronco Hematopoéticas.

Métodos: Trata-se de uma *Scoping Review*, orientada a partir do método proposto pelo *Joanna Briggs Institute*, e seguiu as recomendações do *Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews*. A busca pelos estudos foi realizada entre os meses de julho e agosto de 2020 e ocorreu nas bases de dados e em portais de teses e dissertações nacionais e internacionais.

Resultados: A amostra final foi composta por 71 artigos científicos, todos na língua Inglesa. Houve destaque para o ano de 2018 com 14 (19%) publicações. Observou-se prevalência de estudos realizados nos Estados Unidos da América com 29 (40,8%). No tocante a população, todos (100%) os artigos são sobre pacientes submetidos ao transplante de células-tronco hematopoéticas que apresentaram neurotoxicidades. Acerca

[1]Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil.
Conflicts of interest: nothing to declare.

dos quimioterápicos utilizados no regime de condicionamento pré-transplante de células-tronco hematopoéticas sete (9,8%) utilizaram a combinação de Fludarabina e Ciclofosfamida, seguida da Ciclosporina e Tacrolimus em seis (8,4%), ciclosporina em quatro (5,6%), Fludarabina em três (4,2%). Quanto às neurotoxicidades apresentadas em pacientes submetidos ao transplante, evidenciou-se a síndrome de encefalopatia reversível posterior em 19 (26,7%) estudos. Cabe ressaltar que outros estudos identificaram essa síndrome, porém relataram sintomas diferentes.

Conclusão: As neurotoxicidades apresentadas por pacientes submetidos ao transplante de células-tronco hematopoéticas, são encefalopatia reversível posterior, leucoencefalopatia reversível posterior, encefalopatia de Wernicke, encefalopatia hipertensiva, encefalopatia metabólica, encefalopatia límbica, complicações hemorrágicas e convulsões.

Resumen

Objetivo: Mapear los tipos de neurotoxicidades en pacientes sometidos al trasplante de células madre hematopoyéticas.

Métodos: Se trata de una *Scoping Review*, orientada a partir del método propuesto por *el Joanna Briggs Institute*, que siguió las recomendaciones del *Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews*. La búsqueda de los estudios se realizó entre los meses de julio y agosto de 2020 y ocurrió en las bases de datos y en portales de tesis de doctorado y maestría nacionales e internacionales.

Resultados: La muestra final estuvo compuesta por 71 artículos científicos, todos en lengua inglesa. Se destacó el año 2018 con 14 publicaciones (19 %). Se observó una prevalencia de estudios realizados en Estados Unidos de América con 29 (40,8 %). En lo que se refiere a la población, todos los artículos (100 %) tratan sobre pacientes sometidos al trasplante de células madre hematopoyéticas que presentaron neurotoxicidades. Sobre los quimioterápicos utilizados en el régimen de acondicionamiento previo al trasplante de células madre hematopoyéticas, siete (9,8 %) utilizaron la combinación de Fludarabina y Ciclofosfamida, seguida de la Ciclosporina y Tacrolimus en seis (8,4 %), ciclosporina en cuatro (5,6 %), Fludarabina en tres (4,2 %). Con relación a las neurotoxicidades en pacientes sometidos al trasplante, se evidenció el síndrome de encefalopatía reversible posterior en 19 estudios (26,7 %). Cabe destacar que otros estudios identificaron ese síndrome, pero refirieron síntomas distintos.

Conclusión: Las neurotoxicidades presentadas por pacientes sometidos al trasplante de células madre hematopoyéticas son encefalopatía reversible posterior, leuco encefalopatía reversible posterior, encefalopatía de Wernicke, encefalopatía hipertensiva, encefalopatía metabólica, encefalopatía límbica, complicaciones hemorrágicas y convulsiones.

Introduction

Hematopoietic stem cell transplantation (HSCT) is a therapy indicated for onco-hematological, as well as immunological and autoimmune diseases, and is performed through the transfusion of hematopoietic progenitor cells (HCH), which originate new types of cells due to the undifferentiated and the great capacity for self-renewal. They are obtained by collecting peripheral blood, umbilical cord and placental blood (UCPB) or from the bone marrow.[1]

For this type of procedure, three forms of transplantation can be considered: allogeneic, in which donors can be related or not, but with a compatible Human Leukocyte Antigen (HLA); autologous, when patients are the donors themselves; and syngeneic, in which the cells are from an identical twin brother.[2]

Patients undergoing HSCT becomes susceptible to several complications, which require continuous care from the multidisciplinary team. These complications are classified as acute or chronic, depending on the level of complexity, and extend from pre-grafting, as a result of the conditioning regimen, to the post-transplantation phase. They are presented as possible comorbidities, graft rejection and failure, infections, toxicities, in addition to Graft versus Host Disease (GVHD), specific to allogeneic transplantation.[3]

Some complications affecting the Central Nervous System (CNS) are considered important causes of morbidity and mortality after HSCT.[4-6] Clinical studies report neurological changes in 11 to 59% of patients. Allogeneic transplantation, with donor related or not, and the occurrence of GVHD were the most significant risk factors for the development of neurological complications.[4-7]

Also, some factors that may be related to the etiology of neurotoxicity associated with HSCT are: onset time; symptoms, which are linked to the type of transplant; toxicity of conditioning regimens; vascular complications generated by thrombocytopenia and/or coagulopathy, GVHD; and inadequate immune response.[8]

Immunosuppressive agents administered at the end of the conditioning regimen and that patients use until the post-HSCT period are indispensable for protection against graft rejection and GVHD. However, they are also among the main causes associated with neurotoxicity in allogeneic transplant

recipients. Among the drugs used, calcineurin inhibitors stand out, such as Cyclosporine-A (CsA) and Tacrolimus (TaC), and the estimated incidence of neurotoxicity by TaC is about 30%.[9] Other neurological complications may develop in post-transplant patients, such as cytokine release syndrome (CRS) as well as posterior reversible encephalopathy syndrome (PRES).[9,10]

Such complications are commonly manifested by symptoms such as delirium, encephalopathy, cognitive disorder, dysphasia, tremor, ataxia, myoclonus, focal and sensory motor defect, seizures and cerebral edema.[11] When considering these neurological comorbidities, as well as their prevalence, this study aims to map the types of neurotoxicity presented by patients undergoing HSCT. Therefore, we seek to answer the following guiding question: What is the neurotoxicity presented by patients undergoing HSCT?

Methods

This is a scoping review, guided by the method proposed by the Joanna Briggs Institute (JBI), and following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) recommendations: Checklist and Explanation.[12-14] The review protocol (Annex 1) was registered in the Open Science Framework (OSF) (doi.org/10.17605/OSF.IO/4GA2M).

This type of study aims to investigate the main evidence for a specific area of knowledge, through the research of available scientific productions and possible gaps on the topic addressed.[15] In order to maintain the reliability of the method adopted, the construct was developed in five steps: (1) research question selection; (2) search for relevant studies; (3) study selection; (4) data extraction and analysis; (5) grouping, synthesis and presentation of results.[13]

The first step concerns the research question development, for which the PCC strategy was adopted (P = Population: Patients; C = Concept: Neurotoxic syndromes; and C = Context: HSCT). The guiding question determined for the search for evidence was: What neurotoxicity is presented by patients undergoing HSCT?

Initially, as a way to ensure that there are no studies with the same theme published or registered in the OSF, a broad search was carried out on the platform and in databases for the identification of protocols or reviews with a similar theme. From this diagnosis, the steps to consolidate the scoping review were followed.

To fulfill the second stage and also gather a greater number of studies related to the research object, two distinct search strategies were outlined: patients AND neurotoxicity syndromes OR (nervous system intoxication OR neurotoxicity syndromes) AND bone marrow transplantation OR (transplantation, bone marrow), and (patients AND neurotoxicity syndromes OR (nervous system intoxication OR neurotoxicity syndromes) AND hematopoietc stem cells transplantation OR (stem cell transplantations). Descriptors and synonyms in English were defined by the Medical Subject Headings (MeSH) and in Portuguese by the Descriptors in Health Science (DeCS). Boolean operators AND and OR were used.

The searches took place between July and August 2020 in the following bases: U.S. National Library of Medicine (PubMed), Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Science Direct, *PsycInfo*, and Latin American Literature in Health Sciences (LILACS). Gray literature was rescued by searching The National Library of Australia's Trove (Trove), the only repository that presented results in a previous search carried out to determine the research trajectory. It is worth mentioning that the databases and repositories have particularities, so the strategies used underwent minor adjustments when necessary. Moreover, similarities of the crossings remained maintained and the free full text filter was used when it was available (Chart 1).

Studies that met the research objective and answered the guiding question and that were available in full through the remote access of the Federated Academic Community (CAFe

Chart 1. Search strategies used in theses and dissertations databases and repositories

Database or Repository	Search strategy used
PubMed	#1: ((((patients[MeSH Terms]) AND (neurotoxicity syndromes[MeSH Terms])) OR (nervous system intoxication[MeSH Terms])) OR (neurotoxicity syndromes[MeSH Terms])) AND (bone marrow transplantation[MeSH Terms])) OR (transplantation, bone marrow[MeSH Terms])))) #2: ((((patients[MeSH Terms]) AND (neurotoxicity syndromes[MeSH Terms])) OR (nervous system intoxication[MeSH Terms])) OR (neurotoxicity syndromes[MeSH Terms])) AND (hematopoietc stem cells transplantation[MeSH Terms])) OR (stem cell transplantations[MeSH Terms]))))
Scopus	#1: (KEY ("patients") AND KEY ("neurotoxicity syndromes" OR "nervous system intoxication" OR "neurotoxicity syndromes") AND KEY ("bone marrow transplantation" OR "transplantation, bone marrow")) #2: (KEY ("patients") AND KEY ("neurotoxicity syndromes" OR "nervous system intoxication" OR "neurotoxicity syndromes") AND KEY ("hematopoietc stem cells transplantation" OR "stem cell transplantations"))
CINAHL	#1: (patients) AND (neurotoxicity syndromes OR nervous system intoxication OR neurotoxicity syndromes) AND (bone marrow transplantation OR transplantation, bone marrow) #2: (patients) AND (neurotoxicity syndromes OR nervous system intoxication OR neurotoxicity syndromes) AND (hematopoietc stem cells transplantation OR stem cell transplantations)
Web of Science	#1: TS=(patients) AND TS=(neurotoxicity syndromes OR nervous system intoxication OR neurotoxicity syndromes) AND TS=(bone marrow transplantation OR transplantation, bone marrow) #2: TS=(patients) AND TS=(neurotoxicity syndromes OR nervous system intoxication OR neurotoxicity syndromes) AND TS=(hematopoietc stem cells transplantation OR stem cell transplantations)
Science Direct	#1: (SU (patients) AND (SU (neurotoxicity syndromes OR nervous system intoxication OR neurotoxicity syndromes) AND (SU (bone marrow transplantation OR transplantation, bone marrow)) #2: (SU (patients) AND (SU (neurotoxicity syndromes OR nervous system intoxication OR neurotoxicity syndromes) AND (SU (hematopoietc stem cells transplantation OR stem cell transplantations))
PsycInfo	#1: (MeSH: patients) AND (MeSH: neurotoxicity syndromes OR MeSH: nervous system intoxication OR MeSH: neurotoxicity syndromes) AND (MeSH: bone marrow transplantation OR MeSH: transplantation, bone marrow) #2: (MeSH: patients) AND (MeSH: neurotoxicity syndromes OR MeSH: nervous system intoxication OR MeSH: neurotoxicity syndromes) AND (MeSH: hematopoietc stem cells transplantation OR MeSH: stem cell transplantations)
LILACS	#1: patients [*Descritor de assunto*] AND neurotoxicity syndromes [*Descritor de assunto*] AND bone marrow transplantation [*Descritor de assunto*] #2: patients [*Descritor de assunto*] AND neurotoxicity syndromes [*Descritor de assunto*] AND hematopoietc stem cells transplantation [*Descritor de assunto*]
Trove	#1: ("patients") AND ("neurotoxicity syndromes" OR "nervous system intoxication" OR "neurotoxicity syndromes") AND ("bone marrow transplantation" OR "transplantation, bone marrow") #2: ("patients") AND ("neurotoxicity syndromes" OR "nervous system intoxication" OR "neurotoxicity syndromes") AND ("hematopoietc stem cells transplantation" OR "stem cell transplantations")

- *Comunidade Acadêmica Federada*), through the Journals portal of the Coordination for the Improvement of Higher Education Personnel (CAPES - *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*) of the Ministry of Education (MEC) were included. Editorials, letters to the editor and opinion articles were not included. It is noteworthy that duplicate studies were considered only once.

In the third stage, studies were pre-analyzed from the reading of title and abstract with eligibility criteria application. This phase was carried out by two researchers independently. The fourth stage was marked by the reading of studies in full for data extraction, also independently by three researchers. In cases of disagreement, there were collective discussions to reach consensus among the authors and to exclude doubts.

The articles' title and authors were used to differentiate them at the time of data extraction, which were arranged in a spreadsheet in Excel Microsoft Office®, with extraction of language, year of publication, country of study, research audience, study objective, methodological design, level of evidence, conditioning regimen (chemotherapeutic agents) and types of neurotoxicity presented by patients undergoing HSCT, according to the recommendations of Arksey and O'Malley.[15] The level of evidence was classified according to the JBI.[12]

The collected data were organized and analyzed descriptively, through the presentation of relative and absolute frequencies. The results are arranged in a figure and a chart, and were discussed with the support of literature on the subject, which represents the fifth stage of the method adopted. To differentiate the studies, they received a letter of the alphabet followed by an Arabic number to identify them, such as A1, A2, A3, ..., etc. It should be noted that the list of studies that composed the final sample, as well as their respective references, is attached to the OSF platform.

There was no need for ethical assessment, as the material used is considered to be in the public domain because it is secondary data. However, it is important to highlight that copyrights were respected with correct citation and referencing.

Results

The final sample consisted of 71 scientific articles, this figure represents 46% of the total of 153 pre-selected studies in the reading phase in full, as shown in the flowchart shown in Figure 1.

With regard to the methodological approach, all the studies analyzed had a quantitative approach (100%) and were presented in English (100%). Regarding the country of origin, the prevalence of studies conducted in the United States (USA) (29; 40.8%) was identified, followed by Italy (10; 14.08%), China (6; 8.45%), Brazil (4; 5.63%); Japan (3; 4.22%), France, Austria, South Korea, United Kingdom and Poland, with two studies each (2.81%), Greece, the Netherlands, Canada, Egypt, Russia, Turkey, Pakistan, Spain and Romania, with one publication each (1.40%).

Regarding the year of publication, 2018 (13; 18.30%) stood out, followed by 2020 (9; 12.68%) and 2019 (9; 12.68%), 2017 (6; 8.45%), 1997 and 2015, with four (5.63%) studies each, 2004, 2008 and 2013, with three (4.22%) studies each, 2000, 2010, 2014 and 2016, with two (2.81%) publications each, and 1996, 1998, 1999, 2001, 2003, 2006, 2007, 2009 and 2011, with one study (1.40%) each.

Regarding the methodological classification, there was an emphasis on literature reviews, representing 28 (39.4%) of the analyzed works, descriptive observational method, representing 22 (30.9%), retrospective, representing 16 (22.5%), descriptive, representing two (2.8%), quasi-experimental, representing two (2.8%), and prospective, representing one (1.4%). Regarding the level of evidence, three (4.2%) articles fall within the level of evidence I, within III, 16 (22.5%), within IV, 47 (66.1%), and within V, 5 (6.7%).

Regarding the level of evidence, five (7.04%) were classified as level I (A14, A15, A19, A67, A71), 16 (22.53%) with level III (A3, A6, A20, A22, A28, A30, A37, A47, A51, A52, A59, A60, A62, A65, A66, A69), 47 (66.19%) with level of evidence IV and three (4.22%) with level V.

Regarding the study population, all (100%) articles are about patients undergoing HSCT who presented neurotoxicity. However, some studies reported specificities about the population, of which 26 (36.6%) studies did not mention the type of HSCT performed; 14 (19.7%) corresponded to studies on chimeric T cell antigen receptor (T-CAR) therapy; nine (12.6%) reported that the HSCT had been allogeneic; six (8.4%) reported patients with B-cell malignancies; four (5.6%) revealed patients

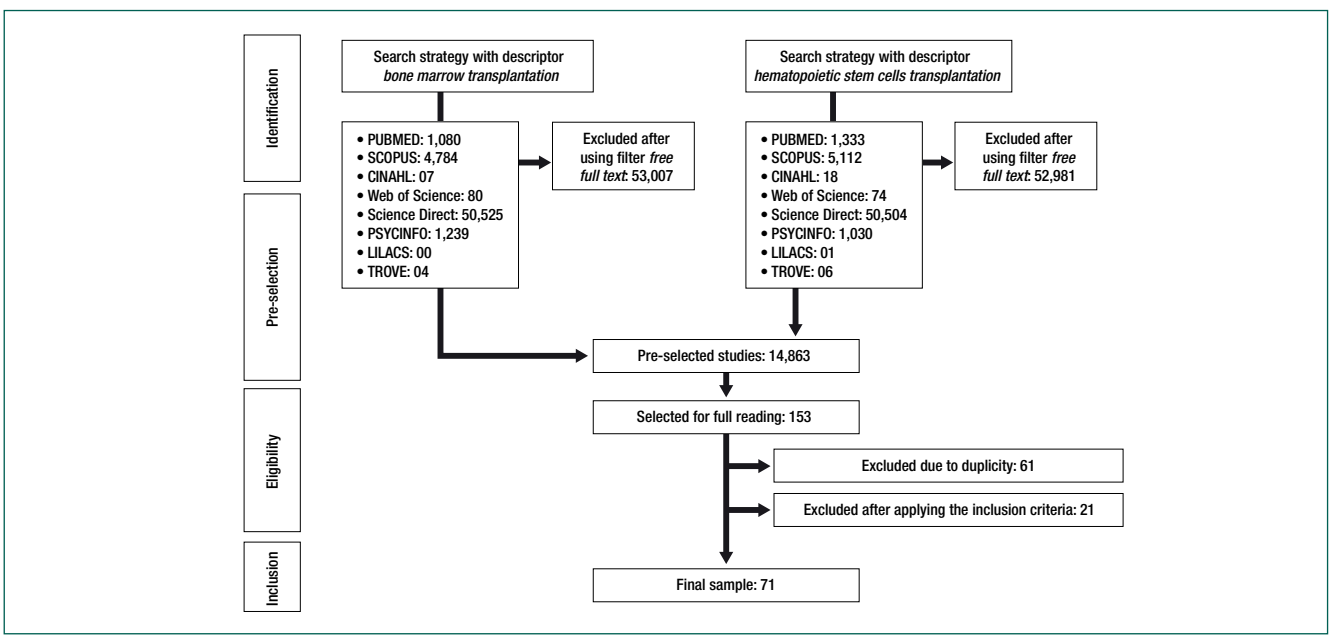

Figure 1. Flowchart of selection of studies that composed the research

with hematological cancer; three (4.2%) referred to CAR-T therapy and autologous HSCT patients; two (2.8%) were patients with PRES; two (2.8%) had autologous HSCT; one (1.4%) described neurotoxicity; one (1.4%) explained about patients undergoing autologous and allogeneic HSCT; one (1.4%) cited transplant patients who received TaC and Cyclosporine to prevent GVHD; one (1.4%) mentioned individuals with Wernicke's encephalopathy; and one (1.4%) mentioned a patient with post-transplant epilepsy.

As for the chemotherapeutic agents used in the conditioning regimen in the pre-HSCT phase, it was identified that 16 studies (22.5%) did not report the conditioning regimen used, seven (9.8%) used the combination of Fludarabine and Cyclophosphamide, followed by of Ciclosporin and TaC in six (8.4%), Ciclosporin in four (5.6%), Fludarabine in three (4.2%). The remaining 38 (53.5%) articles presented the use of different chemotherapeutic agents.

Regarding the neurotoxicity presented in patients undergoing HSCT, the PRES was evidenced in 19 (26.7%) studies. It is noteworthy that other studies have identified this syndrome, but have reported different symptoms. In addition, we identified events that were not associated with PRES in the studies that make up the final sample.

Chart 2 summarizes the results with regard to neurotoxicity related to the events of PRES, posterior reversible leukoencephalopathy, other events and other encephalopathies. The references of the studies that made up the final sample are in Annex 2.

Discussion

Neurotoxicity is an important adverse event and can occur in patients undergoing HSCT in any of its phases. This fact makes it necessary and relevant to map such complications in the literature, which will make it possible to identify their incidence, causality, associated symptoms and will contribute to the scientific basis of professionals working in the area regarding the identification, diagnosis and management of possible cases.

In this sense, when considering the growing scientific production on the subject, in the present research there was a predominance of publications in the USA, with emphasis on the year 2018. This result reflects the use of a new FDA-approved chimeric antigen receptor (CAR) T-cell therapy in 2017.[16]

CAR T-cell therapy consists of the genetic alteration of *in vivo* T-cells expressing an artificial receptor (car), composed of a system that allows specific targeting of an antigen. The extracellular CAR compound is derived from a single-chain variable fragment (monoclonal antibody) that binds to antigens on malignant cells. Before infusing patients, they receive chemotherapy in order to generate immunosuppression and subsequent expansion of CAR T-cells. This procedure can also generate neurotoxicity as an adverse event.[16, 17]

In the meantime, of the results obtained, 36% did not specify the study population, another 8% brought the transplant relationship as a therapy for patients with B-cell malignancies and hematological cancer (5.3%), since HSCT and CAR T-cell therapy are treatment alternatives for hematological and autoimmune diseases.[16-18]

Studies have also shown a higher incidence in allogeneic HSCT and compared it with CAR T-cells.[18,19] Allogeneic transplantation is the most common form of transplantation in the treatment of diseases such as acute lymphoblastic leukemia, non-Hodgkin's lymphoma, aplastic anemia, chronic myeloid leukemia, among others.[18-23]

Thus, from the preparation to the discharge of a patient undergoing this procedure, the main phases are: conditioning, graft infusion, period of pancytopenia, graft infusion and immunosuppression Among these, the conditioning phase corresponds to the period of ablation of recipients' bone marrow and immunosuppression, which can be done through a combination of chemotherapy and irradiation, in addition to the use of immunosuppressive drugs.[20]

Therefore, the findings in the literature reported that the neurotoxicity developed by patients mostly occur as a result of the chemotherapeutic agents used in the conditioning regimen.[21-24] Such

Chart 2. Synthesis of the neurotoxicity highlighted in the analyzed works (n = 71)

Variables	Study code*	n(%) n=71
Events related to PRES		
Headache, visual impairment, disturbance of consciousness, mental status changes, movement disorders and seizures	A1, A6, A7, A13, A15, A23, A34, A36, A39, A40, A48, A50, A51, A52, A49, A64, A66, A67, A70	19(26.76)
Confusion, difficulty finding words, disorientation, aphasia, drowsiness, seizures, or brain swelling	A11, A16, A24, A26, A44	5(7.04)
Difficulty finding words, aphasia, confusion, cognitive impairment, depressed level of consciousness, attention disorders, mental status changes, drowsiness, automatisms, lethargy, dysphasia, dysarthria, tremor, delirium, and/or hallucinations	A8, A25, A29, A68	4(5.63)
Brain disorder affecting white matter, vasogenic changes, reversible focal edematous, headache, nausea and vomiting, seizures, visual disturbances, sensory changes, and occasionally focal neurologic deficit	A31	1(1.40)
Cytotoxic edema without enhancement and confusion	A33	1(1.40)
Delirium, somnolence, obtundation, cognitive disturbance, dysphasia, tremor, ataxia, myoclonus, focal motor and sensory defect seizures, cerebral edema	A38	1(1.40)
Headache, tremor, mild aphasia, mild motor disturbances, intracranial hemorrhage, and fatal rapid-onset diffuse cerebral edema	A42	1(1.40)
Events related to posterior reversible leukoencephalopathy		
Posterior reversible leukoencephalopathy, seizures, ototoxicity, pancerebellar syndrome, necrotizing microangiopathy, transient stroke-like episodes, encephalitis, immune reconstitution inflammatory syndrome, Guillain-Barré syndrome, reversible cerebellar disease, peripheral sensorimotor neuropathy, optic neuropathy and autonomic dysfunction, visual hallucinations, progressive multifocal leukoencephalopathy, mutism, pseudotumor cerebri, brachial plexopathy, hearing loss, cortical blindness, hypertensive encephalopathy, headache, hypomagnesemia, white matter lesions	A4, A45, A54, A57, A69	5(7.04)
Visual disturbances, progressive, peripheral neuropathy, dementia, ataxia, hemiparesis, quadriparesis, and blindness, sometimes leading to coma and death, seizures, varying extents of necrosis, areas of enlarged astrocytes and oligodendrocytes, and multiple lesions	A46	1(1.40)
Intracranial hemorrhages, focal seizures, posterior reversible leukoencephalopathy syndrome, focal neurologic deficit, seizures, and strabismus	A35	1(1.40)
Seizures, cerebellar ataxia, cerebral atrophy, intracranial hemorrhage, and oculomotor nerve palsy	A17	1(1.40)
Other events		
Convulsions, mental confusion, infectious encephalitis, headache, writing difficulty, aphasia, brain swelling, delirium, decreased level of consciousness, language disorder, apraxia, lethargy, myoclonus, obtundation	A9, A10, A12, A22, A37, A41, A58, A62	8(11.26)
CRS and leukoencephalopathy	A59, A61, A71	3(4.22)
Bleeding complications, thrombocytopenia, coagulopathies, cerebral infarction, fungal neuropathology, Wernicke's encephalopathy, altered mental status, ataxia and ophthalmoplegia	A2, A55	2(2.81)
Mental confusion, cognitive impairment, headache, tremor, Guillain-Barré syndrome, aphasia and seizures	A19, A20	2(2.81)
Seizures, loss of vision in the absence of local pathology, altered level of consciousness (ALOC), involuntary movements, ataxia, paresis, cranial nerve palsy, speech impairment, and delirium	A5	1(1.40)
Reversible neurotoxicity, headache, emesis, and transient limb muscle clonus	A14	1(1.40)
Moderate cerebellar syndrome, central neuropathy, peripheral neuropathy, hemiparesis and facial palsy	A18	1(1.40)
Mental confusion, fatigue, seizures, tremors, hyperesthesia/paresthesia, spinal demyelination, coma, cortical blindness, transient speech loss, and cerebellar syndrome	A21	1(1.40)
Severe neurotoxicity, seizures, leukoencephalopathy, hallucinations and cortical blindness	A53	1(1.40)
Demyelination	A28	1(1.40)
Mental confusion, disorientation, impaired responsiveness, visual hallucinations, delusions, motor and/or generalized seizures, changes in mental status and/or level of consciousness, peripheral nervous system changes, pyramidal motor weakness, tremor, cortical blindness, aphasia, and ataxia	A56, A60, A63, A65	4(5.63)
Other encephalopathy		
Wernicke's encephalopathy (mental, eye, and balance disorders)	A43	1(1.40)
Metabolic encephalopathy, intracranial hemorrhage, epileptic seizures, CNS infections, brain abscesses, cerebral infarction, posterior reversible leukoencephalopathy syndrome, movement disorder, Wernicke's encephalopathy and neuroleptic syndrome	A32	1(1.40)
Reversible encephalopathy syndrome, intracranial hemorrhage, cerebral venous sinus thrombosis, CNS infection, leukoencephalopathy, bruising and brain parenchyma	A30	1(1.40)
Limbic encephalopathy, cerebrovascular complications (subdural hematoma, subarachnoid hemorrhage), encephalopathy, invasive aspergillosis, hemophagocytic syndrome, and leukoencephalopathy	A27	1(1.40)
Metabolic encephalopathy, intracranial hemorrhage, ischemic stroke, PRES, seizures, and neuropathy	A47	1(1.40)
Metabolic encephalopathy, posterior reversible leukoencephalopathy, visual disturbances, cortical blindness, CNS infection, cerebral toxoplasmosis infection, bacterial meningitis, intracerebral abscesses, meningoencephalitis, multiple hemorrhages, cerebral, transient ischemic attacks, headache, visual disturbances, and tremor	A3	1(1.40)

toxicity comes from the release of cytokines by drugs used in the prevention of GVHD, a possible event of reaction to the graft infused into recipients.[20, 23] In 10.6% of the articles, the combination of Fludarabine and Cyclophosphamide, the most commonly used lymphodepleting chemotherapy before the infusion of CAR T-cell in order to expand them. It is noteworthy that it is already possible to find studies associating lymphodepleting therapy, in line with the use of Fludarabine and other drugs, with an indirect role in neurotoxicity, since patients often present with CRS, considered

a systemic inflammatory response resulting from the activation and proliferation of CAR T-cells, and predominance of PRES. [25-27]

Regarding PRES, exposure to immunosuppressive or cytotoxic agents and autoimmune diseases are among some of its triggering factors. Moreover, it is characterized by an endothelium injury due to acute hypertension with failure of CNS autoregulation and blood-brain barrier disruption leading to vasogenic edema. [28,29] PRES symptoms are commonly nonspecific, which responds to the symptomatological variants addressed in the results. However, when clear, the most expressive are headache, changes in the level of consciousness, seizures, visual disturbances and focal neurological deficits. It is also worth noting that these are manifested for a short period, considering that such syndrome is considered reversible. However, in case of late diagnosis and treatment, there is risk of serious complications and permanent neurological damage. [28,30]

Additionally, the Nervous System (SN) may also suffer other injuries and complications as a result of the side effects of chemotherapy and/or irradiation, such as possible infections due to post-transplant immunosuppression, compromise of the underlying disease and consequent failure of other systems. [19]

Thus, for health professionals, understanding the specifics of the stages of transplantation, as well as the adverse events to which patients are susceptible is essential for a safe management and development of strategies for identifying and controlling neurotoxicity associated with the HSCT process, in order to improve clinical outcome and survival rates.[1, 31]

As the nurse-patient-family relationship is closer, when compared to other professionals, complications after such procedures require, therefore, differentiated attention and care by the nursing team, with regard to the construction of therapeutic plans, interventions and guidance to patients undergoing transplantation and their caregivers.[1, 31]

Conclusion

Based on the findings, the most common neurotoxicity presented by patients undergoing HSCT are posterior reversible encephalopathy, posterior reversible leukoencephalopathy, Wernicke's encephalopathy, hypertensive encephalopathy, metabolic encephalopathy, limbic encephalopathy, bleeding complications and seizures. It was observed that the neurotoxicity identified in the research are related to several events that vary from moderate to severe complications in the nervous system. Furthermore, other events were detected, but not related to encephalopathies. It is also noticed that the syndromes are closely related to the use of certain chemotherapeutic agents used in the pre-transplant conditioning regimen. Despite the growing number of research on neurotoxicity in patients undergoing HSCT, it is necessary to invest in studies with a high level of evidence so that new drugs that do not result in neurotoxicity are tested, in order to systematize assistance regarding the rapid identification and treatment of these events. It is indicated as a contribution the summary of neurotoxicity presented by patients undergoing HSCT and the chemotherapeutic agents of the conditioning regimen used in patients who presented these syndromes, which allows the organization, planning and development of actions to minimize the occurrence of these complications. Thus, it is believed that this work can encourage the development of new research on the toxicity in the CNS caused by chemotherapeutic agents used in the pre-transplant phase, since this knowledge can help to reduce damage caused to patients. It is pointed out as a study limitation the description of various events in the CNS that were not defined as manifestations of encephalopathies; however, they were characterized as symptoms of neurotoxicity in the studies analyzed. In addition, a portal of journals that presented functional problems in accessing the page during the search for studies.

References

1. Azevedo IC, Cassiano AN, Carvalho JB, Júnior MA. Nursing care for hematopoietic stem cell transplant recipients and their families. Rev Rene. 2017;8(4):559-66.

2. Kurauchi GR, Ono DH, Souza LR, Lourenço GF, Joaquim RH. Percepções de pacientes submetidos ao transplante de células-tronco hematopoiéticas acerca da intervenção em um grupo de atividades de Terapia Ocupacional. Rev Saúde. 2020;46(1):1-13.

3. Pasquini R, Coutinho E. Fundamentos e Biologia do Transplante de Células-Tronco Hematopoéticas. In: Zago MA, Falcão RP, Pasquini R. Tratado de Hematologia. Rio de Janeiro: Atheneu; 2013. pp. 711-29.
4. An K, Wang Y, Li B, Luo C, Wang J, Luo C, et al. Prognostic factors and outcome of patients undergoing hematopoietic stem cell transplantation who are admitted to pediatric intensive care unit. BMC Pediatr. 2016;16:138.
5. Lee YJ, Yum MS, Kim EH, Kim MJ, Kim KM, Im HJ, et al. Clinical Characteristics of Transplant-associated Encephalopathy in Children. J Korean Med Sci. 2017;32(3):457-64.
6. Maffini E, Festuccia M, Brunello L, Boccadoro M, Giaccone L, Bruno B. Neurologic complications after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2017;23:388-97.
7. Cordelli DM, Masetti R, Zama D, Toni F, Castelli I, Ricci E, et al. Central nervous system complications in children receiving chemotherapy or hematopoietic stem cell transplantation. Frontiers Pediatr. 2017;5:105. Review.
8. Dulamea AO, Lupescu IG. Neurological complications of hematopoietic cell transplantation in children and adults. Neural Regen Res. 2018;13(6):945-54. Review.
9. Maffini E, Festuccia M, Brunello L, Boccadoro M, Giaccone L, Bruno B. Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2017;23(3):388-97. Review.
10. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38. Review.
11. Gavriilaki E, Sakellari I, Gavriilaki M, Anagnostopoulos A. A New Era in Endothelial Injury Syndromes: Toxicity of CAR-T Cells and the Role of Immunity. Int J Mol Sci. 2020;21(11):3886. Review.
12. The Joanna Briggs Institute (JBI). Joanna Briggs Institute reviewers' manual: 2016 edition. Australia: JBI; 2016 2018 [cited 2020 Dec 4]. Available from: https://nursing.lsuhsc.edu/JBI/docs/ReviewersManuals/Scoping-.pdf
13. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
14. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018;169(7):467-73.
15. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005;8(1):19–32.
16. Graham C, Hewitson R, Pagliuca A, Benjamin R. Cancer immunotherapy with CAR-T cells - behold the future. Clin Med (Lond). 2018;18(4):324-8.
17. Hopfinger G, Jäger U, Worel N. CAR-T Cell Therapy in Diffuse Large B Cell Lymphoma: Hype and Hope. Hemasphere. 2019;3(2):e185. Review.
18. Li C, Zhang Y, Zhang C, Chen J, Lou X, Chen X, et al. Comparation of CART19 and autologous stem-cell transplantation for refractory/relapsed non-Hodgkin's lymphoma. JCI Insight. 2019;5(17):e130195.
19. Pennisi M, Jain T, Santomasso BD, Mead E, Wudhikarn K, Silverberg ML, Batlevi Y, et al. Comparing CAR T-cell toxicity grading systems: application of the ASTCT grading system and implications for management. Blood Adv. 2020;4(4):676-86.
20. Zétola VH. Investigação de Neuropatia periférica no período recente do transplante de medula óssea [dissertação]. Curitiba: Universidade Federal do Paraná; 1997.
21. Hefzy HM, Bartynski WS, Boardman JF, Lacomis D. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. AJNR Am J Neuroradiol. 2009;30(7):1371-9.
22. Azevedo IC, Ferriera Júnior MA, Aquino LAP, Oliveira AA, Cruz GKP, Cardoso AIP, et al. Epidemiologic profile of patients transplanted with hematopoietic stem cells in a reference service in the State of Rio Grande do Norte, Brazil. Transplant Proc. 2018;50(3):819-23.
23. Iguchi A, Kobayashi R, Yoshida M, Kaneda M, Watanabe N, Cho Y, et al. Neurological complications after stem cell transplantation in childhood. Bone Marrow Transplant. 1999;24:647-52.
24. Nash RA, Piñeiro LA, Storb R, Deeg HJ, Fitzsimmons WE, Furlong T, et al. FK506 in combination with methotrexate for the prevention of graft-versus-host disease after marrow transplantation from matched unrelated donors. Blood. 1996;88(9):3634-41.
25. Sievers S, Watson G, Johncy S, Adkins S. Recognizing and Grading CAR T-Cell Toxicities: an advanced practitioner perspective. Front Oncol. 2020;10:885. Review.
26. Torre M, Solomon IH, Sutherland CL, Nikiforow S, DeAngelo DJ, Stone RM, et al. Neuropathology of a Case With Fatal CAR T-Cell-Associated Cerebral Edema. J Neuropathol Exp Neurol. 2018;77(10):877-82.
27. Cao J, Wang G, Cheng H, Wei C, Qi K, Sang W, et al. Potent anti-leukemia activities of humanized CD19-targeted Chimeric antigen receptor T (CAR-T) cells in patients with relapsed/refractory acute lymphoblastic leukemia. Am J Hematol. 2018;93(7):851-8.
28. Hinduja A. Posterior Reversible Encephalopathy Syndrome: Clinical Features and Outcome. Front Neurol. 2020;11:71. Review.
29. Picchi E, Di Giuliano F, Marziali S, Minosse S, Ferrazzoli V, Da Ros V, et al. Radiological findings of Posterior Reversible Encephalopathy Syndrome in transplanted children previous affected by hemoglobinopathy: a neuroimaging retrospective analysis. Eur J Radiol Open. 2019;6:144-51.
30. Cordelli DM, Masetti R, Zama D, Toni F, Castelli I, Ricci E, et al. Central Nervous System Complications in Children Receiving Chemotherapy or Hematopoietic Stem Cell Transplantation. Front Pediatr. 2017;5:105. Review.
31. Paton EJ, Coutinho MA, Voltarelli JC. Diagnóstico e tratamento das complicações agudas do transplante de células progenitoras hematopoéticas. Medicina (Ribeirão Preto). 2000;33:264-77.