

Late complications of children and adolescents after allogeneic hematopoietic stem cell transplantation: An integrative review

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Abstract

Purpose: Patients undergoing Allogeneic hematopoietic stem cell transplantation (allo HSCT) can develop late complications that limit their functioning and reduce their quality of life. This phase requires nursing-specific knowledge for care plans that can meet the patient's real needs. For this reason, the purpose of this review is to compile the data available in the literature on late complications present in the follow-up of pediatric and adolescent patients after allo HSCT.

Methods: An integrative review following Cooper's methodology and the PRISMA guidelines. The search was carried out on PubMed, Scielo, and BIREME. All articles that described long-term complications on pediatric and adolescents allo HCT survivors were included.

Results: Of the 9,783 reviewed publications, 52 met the inclusion criteria. The most frequent long-term complication mentioned was endocrine, followed by pulmonary, cardiovascular, ocular dysfunctions, and secondary neoplasias. Risk factors for late complications after allo HSCT are total body irradiation, chronic graft-versus-host disease, conditioning regimen, gender, donor type, previous therapy, and age at transplant.

Conclusions: With the increased survival, the number of patients living with late complications is growing too. The endocrine complications were the most frequent late complication identified in the studies and can impair quality of life, and demand increasing attention. This knowledge can support develop a tool for assessment and, based on that, creating an individualized care plan focused on the real needs of these patients.

Keywords: Bone marrow transplant, Allogeneic, Late complications, Integrative review

Introduction

Allogeneic hematopoietic stem cell transplantation (allo HCT) has been used to treat malignant and non-malignant hematologic diseases for many years. Despite offering the best chance of survival for many children, it can at the same time lead to long-term complications due to chemotherapy and irradiation used in preparative regimens [1,2].

It was estimated that there will be 502,000 survivors of transplantation by 2030 and 14% of them would be under 18 years of age at the time of transplant [1]. As the number of allo HSCT survivors increases, the late effects and chronic health conditions are more frequent. These indices range from 30 to 60% in patients with an average follow-up of 5 to 15 years, with a progressive increase in risk over time [3]. Chronic graft versus host disease (cGVHD) contributed significantly to the increased risk of severe or life-threatening conditions, and more importantly, to the development of multiple chronic conditions [3]. Other risk factors for late effects in HSCT survivors include younger age at HSCT and the use of total body irradiation (TBI) [4].

Transplantation during childhood years can predispose children to late toxicities and consequently,

increased morbidity and mortality compared with age and sex-matched counterparts [5].

It is important to note that patients previously treated for malignancy have a cumulative exposure to chemotherapy which may, in turn, account for some of the consequences attributed to the long-term effects of HSCT [6].

Because of the unpredictable, complex, and multifactorial nature of these long-term and late effects in HSCT survivors means that patients require regular life-long assessments guided by rigorous protocols [7]. The care plans can give specific attention to the real needs of the patient at this stage, developing educational actions for the patient and family [7]. Unfortunately, the studies involving the care of post allo HSCT patients are poor, and this knowledge will facilitate the development of appropriate intervention programs to alleviate the long-term effects of HSCT on pediatric quality of life [8].

So, for this reason, the purpose of this integrative review aims to compile the data available in the literature on late complications present in the follow-up of pediatric and adolescents patients after allo

HSCT. The following research question guided the search on which the review was based: What are the most frequent late complications in pediatric and adolescent patients after allogeneic hematopoietic stem cell transplantation?

Methods

Design

This is an integrative review of the literature adopted the five-step methodology proposed by Cooper [9] and updated by Whittemore [10], which includes: (a) formulation of the problem, (b) literature search, (c) evaluation of data, (d) data analysis and interpretation, and (e) presentation of findings. The integrative review is a type of research review method allowing the simultaneous inclusion of experimental and non-experimental research to, more fully understand a phenomenon of concern [10]. This integrative review was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [11] and the search process is conceptualized in the PRISMA flow diagram [12] (Figure 1).

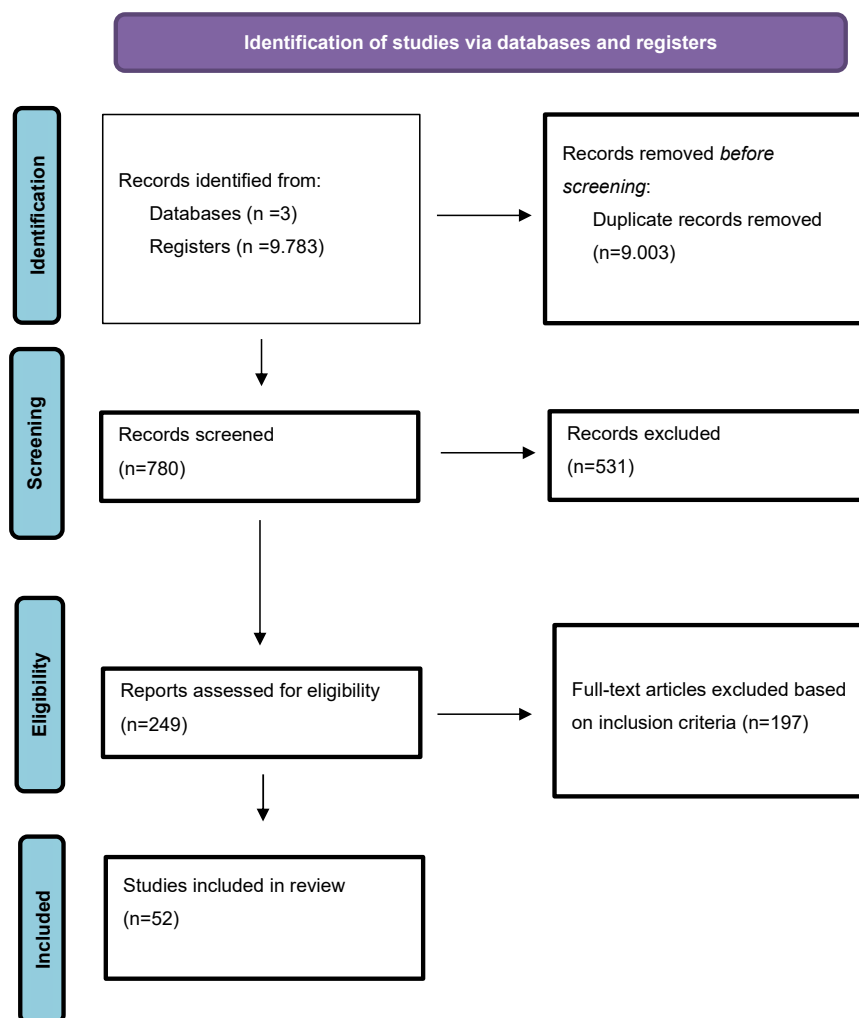


Figure 1. PRISMA 2020 flow diagram [11].

Search strategy

For search strategy, it was established a combination of the following MeSH terms and DeCs: “bone marrow cell transplantation”, “hematopoietic stem cell transplantation”, “late effects” and “late complications” with the addition of the Boolean operator “AND”.

The electronic search was made using the following databases: National Library of Medicine (PubMed), Scientific Electronic Library Online (SCIELO), and Latin American and Caribbean Center on Health Sciences Information (BIREME).

Study selection

It was included published research focused on late complications on allo HCT until December 2020, published in English, Spanish or Portuguese; and with free full access. Review articles, dissertations, letters, theses, opinions or perspectives, and commentaries were excluded. Research studies with autologous HCT patients were also excluded.

Analysis

After finding the studies, they were screened by title and abstract. The texts were fully read and analyzed considering the year and place of publication, language, study design, objectives, sample, types of late complications, and outcomes in each identified theme. The duplicate articles were removed and the software program Excel was used to organize and code the articles to facilitate the review. As for ethical aspects, all information extracted from the articles belongs to the public domain.

Results

Study characteristics

The study was conducted from November to December 2020. The first search registered 9,783 articles. After removing duplicate articles and applying the inclusion and exclusion criteria, a total of 52 articles were included (Figure 1).

All selected articles were written in English. The articles were published between 1990–2020 and most articles were published between 2010 and 2020 ($n=34$).

The majority of publications is grouped in the United States of America ($n=11$), followed by Japan ($n=7$) and The Netherlands ($n=6$). There is one Brazilian study. Seven publications were multicenter, including data from big data centers such as the Center for International Blood and Marrow Transplant Research (CIBMTR).

Patients and late complications

In the studies, patient's age at the time of HSCT ranged from 0.1 to 21 years, and the time after HSCT ranged from 1 to 39 years after HSCT. Both patients who had the malignant disease and those who had non-malignant diseases had late complications.

Figure 2 is the distribution of articles by late complications identified. The most frequent long-term complication mentioned was endocrine, cited in 28 studies, documented from 10 to 91% of the patients in studies. The complications in the endocrine system described in studies are summarized in Table 1.

The second most frequent is a pulmonary complication, described in 18 studies and the frequency in the population studied ranged from 0 to 81%, following by cardiovascular complication, in 14 studies and frequency ranged from 2 to 26%, ocular and secondary neoplasias, described in 13 studies each, and frequency ranged from 5 to 69% and 2 to 13%, respectively.

Some complications, although frequent in the sample studied, there were a few articles about them, such as psychological e cognitive complications (ranging from 0 to 77% and 9 to 85%, respectively).

Risk factors more related to late complications allo HCT were TBI (described 23 articles) and cGVHD and treatment (described in 11 articles). Other risk factors identified in studies are conditioning regimen, gender, type of donor, previous therapy, and age at transplant.

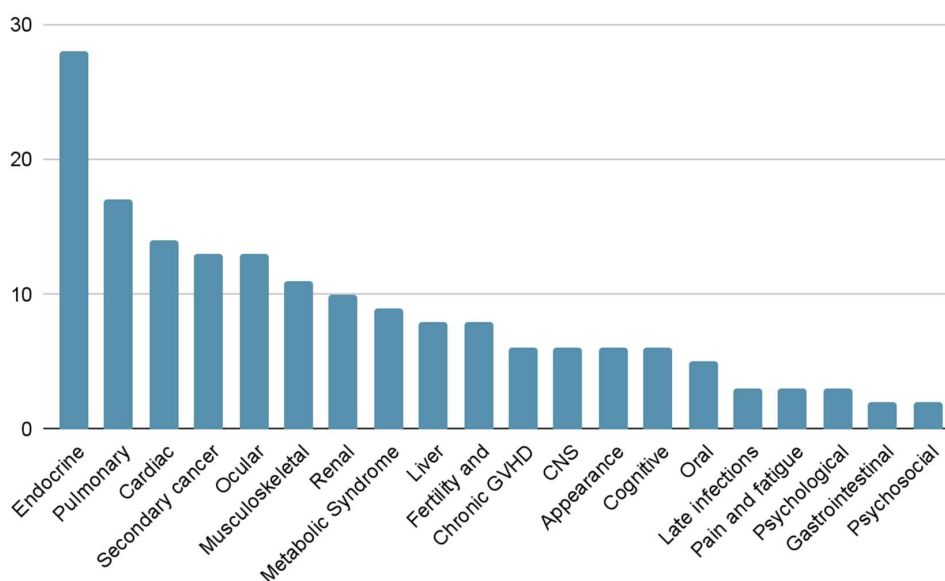


Figure 2. Distribution of articles by late complications identified.

Table 1. Description of the endocrine complications described in articles.			
First author, year, and country	Participants evaluated	Endocrine Complications	Risk factors
van Weel-Sipman et al [13], 1990, The Netherlands	27	Thyroid dysfunction Gonadal/Puberal impairment Growth impairment	- TBI
Hovi et al. [14], 1997, Finland	15	Gonadal/Puberal impairment	- TBI
Hirayama et al. [15], 1998, Japan	1	Diabetes	- TBI and/or splenic irradiation.
Cohen et al. [16], 1999, Sweden	79	Growth impairment	- TBI
Eapen et al. [17], 2000, USA	37	Growth impairment Thyroid dysfunction	- TLI or TBI cyclophosphamide,
Berger et al. [18], 2005, France	388	Thyroid dysfunction	- age at BMT - CR2 (vs CR1) - TBI
Forinder et al. [19], 2005, Sweden	52	Growth impairment	NA
Leung et al. [20], 2007, USA	155	Thyroid dysfunction Hypogonadism Growth impairment	- younger - age at HCT - TBI
Ferry et al. [21], 2007, France	112	Thyroid dysfunction Gonadal/Puberal impairment Growth impairment	- TBI
Löf et al. [22], 2009, Sweden	53	Growth impairment	NA
Bresters et al. [23], 2010, The Netherlands	162	Thyroid dysfunction Gonadal/Puberal dysfunction Growth impairment	- Older age at BMT - TBI.
Sanders et al. [24], 2011, USA	152	Thyroid dysfunction Gonadal/Puberal dysfunction Growth impairment	- TBI - Chronic GVHD
Tomita et al. [25], 2011, Japan	51	Thyroid dysfunction Gonadal/Puberal dysfunction Growth impairment	- radiotherapy cranial - TBI
Hyodo et al. [26], 2012, Japan	34	Gonadal/Puberal dysfunction	- irradiation and/or alkylating agent before SCT - fatty liver.
Mulcahy Levy et al. [27], 2013, USA	15	Thyroid dysfunction Gonadal/Puberal dysfunction Growth impairment	- TBI
Bresters et al. [28], 2016, EBMT registry	297	Thyroid dysfunction Growth impairment	- TBI
Allewelt et al. [29], 2016, USA	102	Thyroid dysfunction Gonadal/Puberal I impairment Growth impairment	- cGVHD - Steroid therapy - Immunosuppression.
Myers et al. [30], 2016, USA	114	Thyroid dysfunction Gonadal/Puberal dysfunction Growth impairment	- TBI - Alkylating agents

Madden et al. [31], 2016, USA	43	Thyroid dysfunction Gonadal/Puberal dysfunction Growth impairment	- Preparative regimen.
Visentin et al. [32], 2016, France	314	Thyroid dysfunction Gonadal/Puberal dysfunction Growth impairment	- Donor type
Chaudhury et al. [33], 2017, USA, Canada, and Unit Arab Emirates	176	Thyroid dysfunction Gonadal/Puberal dysfunction Growth impairment	- Older age at BMT
Vrooman et al. [34], 2017, CIBMTR registry	717	Thyroid dysfunction Gonadal/Puberal dysfunction Growth impairment	- TBI - Donor type - Stem cell source - Sex female
Rahal et al. [35], 2018, France	99	Thyroid dysfunction Gonadal/Puberal impairment Diabetes Growth impairment	- Age - Iron overload - Preparative regimen - Steroids therapy
Faraci et al. [36], 2019, EBMT registry	137	Gonadal/Puberal impairment	- Alkylating agents
Sutani et al. [37], 2019, Japan	23	Gonadal/Puberal dysfunction Growth impairment	- Preparative regimen - Steroids therapy
Komori et al. [38], 2019, Japan	19	Gonadal/Puberal dysfunction	- TBI
Marinho et al. [39], 2020, Brazil	101	Thyroid dysfunction Gonadal/Puberal impairment Diabetes Growth impairment	- Females - GVHD - TBI
Mathiesen et al. [40], 2020, Dinamark and Finland	98	Gonadal/Puberal impairment	- testicular irradiation
Abbreviations: NA: Not Available			

Discussion

In this review, the analyzed studies showed several late complications after allo HCT in children and young adults. The late complication most found in articles was endocrines. The endocrine system is highly susceptible to damage from high-dose chemotherapy and/or irradiation that is given in the conditioning regimen [41]. The specific endocrine organs most affected by HCT include the thyroid gland, the pituitary, gonads, and hormones that support the development and stability of the skeletal [41]. Our review identified the most frequent complications in thyroid dysfunction, gonadal/puberal impairment, and growth impairment.

Thyroid dysfunction is a commonly encountered problem following HCT and has incidence in pediatric patients undergoing HCT between 0 to 52%, depending upon the size of the cohort and the type of transplants performed [41]. It's much higher than generally reported for adult patients, where rates are generally around 15% [41]. Thyroid injury has been associated with the use of myeloablative conditioning regimens where radiation is both dose and delivery-dependent [30]. But this complication can occur in patients that use non-myeloablative conditioning too [30].

Another endocrine complication that affects frequently the pediatric population after HCT is growth impairment, with a prevalence of ranges from 20 to 84% [42]. Although pituitary production of growth hormone (GH) plays an important role in determining final height, many other factors play a role, including nutritional status, thyroid function, corticosteroid therapy, and the production of sex hormones during the pubertal growth spurt. The risk of impaired growth is greatest in the youngest children [41,43].

Gonadal impairment and puberty delays are other common endocrine complications in adolescents and young adults after HCT. Puberty, the phase of life when transgression from childhood to a fertile adult occurs, is complex because of the occurring physical changes and the maturational process of the individual [44]. The pre-pubertal status of the child is the result of an active central regulatory process. The changes in body appearance, body composition, and height growth are the consequences of the sex hormones produced [44]. Normal pubertal development requires a functioning hypothalamic-pituitary-gonadal axis, and high-dose alkylating agents and/or irradiation to the brain or gonads can disturb can affect this process [44,45].

Both sexes can be affected by pubertal delay or failure. Incomplete pubertal development or pubertal failure has been reported to occur in approximately 57% of prepubescent females following HCT and 53% in males [43]. In males, primary gonadal insufficiency is defined as impaired spermatogenesis, testosterone production, or both [46]. And in females is characterized by primary amenorrhoea (pre-pubertal) or secondary amenorrhoea (for >4 months), elevated FSH, and low estradiol [46]. Premature ovarian insufficiency affects more than 75% of female pediatric HSCT recipients [45]. This complication can affect fertility, and the ability to lead full reproductive lives is very important to both female and male HCT survivors [41].

Despite not being a life-threatening complication, infertility is associated with significant psychological distress for HSCT the recipient and his family [47]. In this review, we identified 8 articles describing infertility as such a late complication. Two of these were aimed at determining fertility status and possible risk factors for infertility [48,49].

Among the risk factors identified in the reviewed articles, TBI was the most cited in late complications, principally in patients with endocrine complications. TBI is an important part of conditioning regimens for bone marrow transplantation for hematological malignancies and can achieve better outcomes than regimens not containing TBI [32]. TBI aims to eradicate malignant cells in the same area that chemotherapy does and in sanctuary organs that are not reached by chemotherapy drugs, which are mainly the brain and testes [32].

Beyond TBI, other risk factors were associated with developing late complications as such alkylants agents in the preparative regimen, act at HCT, steroid therapy, and sex [5,43].

Although the treatment before HSCT in patients with the malignant disease was a risk factor, we can note in the studies that patients with malignant disease and those non-malignant diseases can be affected with late complications, and both need attention on late follow-up after HSCT [32]. Patients who do TBI needs more attention, mainly endocrine complications.

It has been identified some complications that, although they have a high incidence in patients after HSCT, few articles describe them, such as psychological e cognitive complications that may not directly impact mortality, but can impair quality of life. Psychological complications include, among others, depression, post-traumatic stress disorder, and neurocognitive deficits. Depression occurs in 12%-30% of HCT survivors and is more frequent in female patients, younger patients, and those with poor social support, history of recurrent disease, chronic pain, and chronic GvHD [50]. Post-traumatic stress disorder occurs in 28% of patients at six months after HCT and may persist for 5%-13% of cases, although its risk factors are not yet clear [50].

Pediatric patients may experience altered behavior patterns, changes in social habits, and changes in academic/school behavior years after HSCT. At the transition from acute convalescence to long-term follow-up, psychological distress may increase rather than abate as the patient and his/her family must cope with changes in roles, employment situations, and financial difficulties [43].

The limitation of this review is the selection of English, Portuguese and Spanish language studies; which may contribute to the exclusion of relevant studies published in other languages.

Conclusions

The endocrine complications were the most frequent late complication identified in the studies and can impair quality of life. It is necessary to consider more studies with complications like cognitive and psychological because these can impair quality of life too. This knowledge can support nursing practices in late follow-up HSCT. Nurses can develop a tool for assessment and, based on that, develop an individualized care plan focused on the real needs of these patients.

Declaration of Conflicting Interests

The Authors declares that there is no conflict of interest.

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