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LITERATURE REVIEW

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Long-term dental follow-up in hematological stem cells transplantation children

Acompanhametnto a longo prazo das alteracoes dentarias em pacientes pediatricos submetidos ao transplante de celulas-tronco hematopoieticas

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ABSTRACT

Objective: The aim of this paper is to update the current published content about the craniofacial long-term development disturbances of childhood hematopoietic stem-cell transplantation (HSCT) and the preparative regimens for the onco-hematological malignancies treatments. **Methods:** Two authors independently reviewed the published articles about long-term effects of childhood HSCT that fitted in to predetermined inclusion/exclusion criteria: clear definition of exposure or intervention, standard outcomes measurement and appropriate statistical analysis. **Results:** Twelve papers matched all the previous established eligibility criteria and were included in this review. The children's age at HSCT were related to a higher risk of dental development disturbances, such as agenesis, dental hypoplasia, root stunting, crown-root proportion alterations, and microdontia. Craniofacial vertical growth was impaired in the irradiated patients without antero-posterior or latero-lateral impairment. Temporomandibular joint dysfunction was found to be more prevalent in the patients diagnosed with graft-versus-host disease. **Conclusion:** The late effects of craniofacial development disturbances

RESUMO

Objetivo: Este artigo visa revisar o conteúdo publicado sobre as alterações tardias em crianças submetidas ao transplante de células-tronco hematopoiéticas (TCTH) e o regime pré-transplante para tratamento das doenças onco-hematológicas. **Método:** Dois autores independentes conduziram uma revisão simples dos artigos recentemente publicados sobre o tema, utilizando os critérios de exclusão/inclusão pré-determinados: definição clara da intervenção clínica realizada, mensuração dos resultados padronizada e análise estatística adequada. **Resultados:** Doze artigos enquadraram-se em todos os critérios de avaliação pré-determinados para esta revisão. Houve correlação entre a idade da criança no momento do TCTH e maior risco de distúrbios de desenvolvimento dentário, como agenesia, hipoplasia dentária, encurtamento radicular, alterações da proporção coroa-raiz e microdontia. Houve alteração do crescimento craniofacial no sentido vertical sem, no entanto, alterar o crescimento anteroposterior e latero-lateral. Disfunção da articulação temporomandibular foi mais prevalente entre os pacientes com diagnostico de Doença do Enxerto contra o Hospedeiro. **Conclusão:** Os efeitos

lead to several aesthetic and functional impairment, periodontal bone resorption with consequent impairment of chewing ability, and risk of early tooth loss often associated with life's quality impairment. Further investigations should be performed to provide accurate information for patients, parents and health care professionals.

KEYWORDS

Dental development; Craniofacial growth; Bone marrow transplantation; Hematopoietic stem-cell transplantation; Chemotherapy; Radiotherapy.

tardios do desenvolvimento craniofacial podem levar a diversas alterações estéticas e funcionais, reabsorção óssea periodontal, diminuição da capacidade de mastigação e perda dentária precoce com possíveis impactos negativos sobre a qualidade de vida. Mais estudos são necessários para fornecer informações precisas aos pacientes, cuidadores e profissionais de saúde.

PALAVRAS-CHAVE

Desenvolvimento dentário; Crescimento craniofacial; Transplante de medula óssea; Transplante de células-tronco hematopoiéticas; Quimioterapia; Radioterapia.

INTRODUCTION

High-dose chemotherapy combined or not combined with radiation-therapy followed by hematopoietic stem cell transplantation (HSCT) is the current treatment for childhood onco-hematological diseases which leads to survival rates increases resulting in more than 30.000/year patients worldwide successfully cured [1]. According to the donor cell source, the HSCT can be classified as autologous, where the donor cell's source comes from the same patient; or allogeneic where hematopoietic stem cells are obtained from related or unrelated donor [2] and the choice of treatment modality depends on several factors related to the patient, the disease and the availability of compatible donor [3]. Currently, a 5-year survival rate for the most common hematologic disease (acute lymphoblastic leukemia) is above 80%. In some groups, this rate may achieve 95% [4].

Nonetheless, the myeloablative regimens pre-HSCT for childhood cancer treatment can lead to several systemic complications concerning endocrine system underdevelopment, heart, lung, kidneys, bones and neurological malformations, growth deficiencies, hypogonadism, premature menopause/andropause, and development of secondary sexual characteristics disorders [5,6].

Between 62-95% of the childhood HSCT survivors will experience some late effect following HSCT and 27-40% will present serious consequences including poorer quality of life, psychosocial impairment and increased high risk of death [7].

Dental development disturbances are widely described as tooth agenesia, microdontia, shortened roots, changes in the dental crown-root proportions root stunting, and V-shaped apex. The first and second premolars or second molars are the more affected teeth seen in HSCT childhood patients, with significantly differences in comparison to healthy individuals [8-12]. Also, there is a positive correlation between the patient's age at the moment of HSCT and the dental development disturbances, with radiotherapy showing positive correlation with higher prevalence of dental and cranial development disturbances [13].

This research main goal is to present an updated review of of the craniofacial development disturbances in childhood HSCT patients for onco-hematological diseases treatments.

RESEARCH METHOD

Search strategies and criteria for selecting studies

The MEDLINE/Pubmed databases of the National Library of Medicine, Bethesda, Maryland, were used to search for appropriate articles addressing the focused question: what are the craniofacial development disturbances and their subsequent late effects among survivors of HSCT for childhood onco-hematological cancer treatment. For this purpose, it was organized a simple review of published manuscripts that discussed the craniofacial development disturbances and their subsequent late effects among survivors of HSCT for childhood onco-hematological cancer treatment.

The following keyword combinations were employed in this review:

- Bone marrow childhood transplantation
- Craniofacial growth
- Craniofacial development;
- Dental development.

Also, the related articles were investigated to ensure a thorough review.

Eligibility criteria

The following eligibility criteria encompassed all the English language published full-articles regarding long-term dento-facial follow-up of childhood-HSCT patients. Letters to the editor, historical reviews and unpublished articles were not included. The exclusion conditions comprised all papers that did not thoroughly presented comprehensive description of chemo and/or radiotherapy; studies within less than 2 years follow-up; case reports or case-series, adult-HSCT, HSCT for solid tumors treatment or congenital diseases.

All the abstracts derived from this search were thoroughly reviewed for relevance. Any dissimilarities between the authors were doubled checked to avoid any misleadings. Hand searching was not carried out.

Data collection

Two authors independently selected and thoroughly evaluated published articles regarding craniofacial development disturbances in childhood HSCT patients. Article's quality was assessed by three criteria: clear definition of exposure or intervention, standard outcomes measurement, and appropriate statistical analysis. Any discrepancy in assessment of validity was resolved by discussion between the authors.

CRITICAL REVIEW

Due to the lack of randomized controlled trials, the results was derived from largely observational studies. Firstly, 120 papers were retrieved. After thorough examination of these abstracts and respective full-text articles, 107 papers were removed from the analysis once this papers did not match the previously established inclusion criteria. Twelve papers matched all the previous established eligibility criteria and were included in this review. Eight of them were cross-sectional studies, two were case-controls, one was a retrospective study, and one was a cohort study.

Dental development disturbances

Dental development disturbances due to childhood HSCT are commonly seen in long-term survivors. The dental alterations induced by HSCT include aesthetic and functional impairment and periodontal bone resorption, resulting in impairment of chewing ability and a greater risk of early tooth loss, thus jeopardizing the long-term maintenance of oral health. In addition, it has been recently suggested that these dental complications could increase the cardiovascular morbidity and mortality rates associated with dental care intervention among survivors [14-15].

Also, a younger age at transplantation and preparative regimens seemed to be related

to a higher risk of developing dental alterations, such as agenesis, dental hypoplasia, root stunting, crown-root proportion alterations, and microdontia. Moreover, total body radiation therapy and high-dose chemotherapy increased the risk of dental development disturbances in HSCT children. However, there is not sufficient evidence to indicate that different chemotherapeutic mieloablative agents solely can have increased effects on dental development [8-15].

Craniofacial development disturbances

Craniofacial and dental abnormalities may affect almost 90% of the individuals who receive high-dose radiotherapy in the head and neck region before the age of 10 years old. These development disturbances in the craniofacial growth are commonly described as a significantly lower linear vertical growth in the alveolar height, with no significant differences in the maxilla and mandibular length. When the antero-posterior growth was considered, HSCT and preparative regimens did not influence the mandible and maxilla vertical growth [16,17].

There are no published data regarding differences among conditioning chemotherapeutic regimens including Busulfan® or total body irradiation, with similar deleterious effects on tooth area reduction and craniofacial parameters. The age of the children at the moment of HSCT and preparative regimens highly influenced the craniofacial growth and development. Again, patients' age at HSCT showed to be more relevant to craniofacial growth impairment. Associated high dose radiation therapy (≥30 Gy) for mieloablative purposes contribute to the extent and severity of bone and soft-tissue deformity [12].

These craniofacial development disturbances may require multiple surgical reconstructions and ultimately can deeply impact quality of life in long-term survivors. Since craniofacial reconstruction techniques have flourished in the last decade, cases are best managed in an individualized manner by a multi-specialty team following an extensive pre-operative planning [18].

Temporomandibular joint dysfunction

Decreased mouth opening range is a common undesired effect of radiation therapy and its functional outcoming are poor oral health, bad nutrition, impaired dental care, and compromised speech functions. The prevalence of Temporomandibular Joint Dysfunction (TMJ) pain and dysfunction in long-term survivors after pediatric bone marrow transplantation (HSCT), conditioned with total-body irradiation (TBI), is usually higher in comparison with the healthy individuals [19].

Children and adolescents submitted to TBI commonly presents reduced mouth opening capacity and poor laterality movements. Both irradiation and chemotherapy induce long-term alterations in connective and muscle tissues, resulting in inflammation and, eventually, fibrosis. These changes in tissue homeostasis and concomitant growth retardation may lead to a observed malocclusion and reduced mobility of the temporomandibular joint, with subsequent muscle pain and headaches, which impairs quality of life perception [20].

Another common cause of TMJ dysfunction in childhood HSCT patients is a limited moth-opening due graft-versus-host disease (GVHD). GVHD is the leading cause of morbidity and non-relapse mortality after childhood HSCT. This early manifestation often leads to several long-term complications in at least half of the patients with chronic graft-versus-host-disease. These manifestations can be presented as oral mucosal lesions, salivary gland dysfunction, or reduction of the mouth opening due to cutaneous sclerosis, and it can be isolated or with different overlapping combinations. The mouth-opening limitations affects approximately 17% (37 of 212) of the patients with cGVHD, considering that most of them show significant correlation between mouth-opening limitations and pain.

Treatment includes early physiotherapy with prophylactic jaw-stretching exercises to prevent progressive fibrosis [19,20].

DISCUSSION AND CONCLUSION

The HSCT is commonly recommended as a treatment measure for hematologic malignancies, bone marrow deficiencies, or congenital disorders of hematopoiesis, such as leukemias, lymphomas, breast tumors, and anemia severe aplastic [21,22]. Five years' survival rate post transplant can vary between 70-90%, whereas in childhood cancer it can exceed 95% [1,23,24]. However, the increase in life expectancy of patients undergoing HSCT is accompanied by an increased incidence of unwanted effects related to treatment. These complications can be acute or chronic [6]. It is estimated that between 62-95% of the surviving HSCT children will experience a late effect resulting from treatment [25,26], and 27-40% an augmented risk of death [27].

This review summarizes the literature on the long-term effects of treatment-related dental development disturbances in survivors of childhood onco-hematological cancer. Only twelve published papers fulfilled the inclusion/exclusion criteria and were evaluated for: type of study, number of individuals (n), preparative regimen therapies, qualitative and quantitative dental development disturbances, follow-up time, and age at HSCT. In addition, data on the purpose, results, and main conclusions were gathered.

Data assembling suggested the age at transplantation seemed to be more risk-related to craniofacial development disturbances than any other factors. Patients who underwent HSCT before 3 years of age have a higher risk of experiencing dental development disturbances and facial growth [14]. The higher incidence of tooth development disorders (agenesia, dental hypoplasia, dental root stunting, crown-root proportion alterations, and microdontia) was found in the permanent upper second premolar and inferior first molars [8-17]. Moreover, in addition to the dental development disturbances, the assembled data showed important late effects resulting from childhood HSCT to the stomatognathic system, such as the temporomandibular joint dysfunction and the vertical craniofacial growth impairment, are described [28].

The effects of craniofacial development disturbances lead to aesthetic and functional impairment, periodontal bone resorption with consequent impairment of chewing ability, and risk of early tooth loss [13,14]. These late effects can result in significant negative impact on life's quality perception [29-31], which can persist for more than 2 years after transplantation [32].

The limitations of the studies included in this review should be considered. First, the cross-sectional observations of childhood cancer may have resulted in selection bias. It is possible that children with adverse dental outcomes were more likely to return for evaluation and care, which could have inflated report estimates. On the other hand, those patients who did not survive long enough to be included in the study groups may have biased the reported dental outcomes toward the null. Furthermore, another review shortcoming is related to largely variable chemotherapeutic mieloablative regimens, leading sometimes to unfeasible statistical studies. To offset this lack of data, further investigations are warranted to provide more accurate information and to help patients and dental care providers to improve the long-term quality of life of HSCT patients, focusing on the late craniofacial development long-term effects.

In conclusion, HSCT has improved the survival rates of childhood cancer patients, but there are several undesired long-term effects that may withdrawn quality of life. A multidisciplinary approach comprising oncologists, nurses, social workers, dietitians, dentists and other health care professionals is essential for childhood onco-hematological cancer treatment to avoid, control and minimize

craniofacial development disturbances that can affect patient's quality of life before, during and after cancer treatment. Proper long-term follow-up dental care for those patients plays an important role in the diagnosis, prevention, and treatment to avoid further complications. More accurate knowledge to dental practitioners are needed and further investigations should be performed to provide accurate information for patients, parents and health care professionals.

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