UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE ODONTOLOGIA

AMANDA DE FARIAS GABRIEL

FATORES DE RISCO ASSOCIADOS AO DESENVOLVIMENTO DE MUCOSITE ORAL EM PACIENTES PEDIÁTRICOS ONCOLÓGICOS

Porto Alegre
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Trabalho de Conclusão de Curso apresentado ao Curso de Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para a obtenção do título de Cirurgião-Dentista.

Orientadora: Profª. Drª. Manoela Domingues Martins

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DEDICATÓRIA

Dedico este trabalho de conclusão de curso a todos que acreditam na pesquisa científica e na educação como forma de mudar o mundo para melhor, especialmente a todas as pesquisadoras mulheres que sempre me inspiraram durante esta trajetória.

AGRADECIMENTOS

À minha mãe, a mulher mais forte e incrível que conheço, a pessoa que mais me apoiou, me incentivou, me ajudou e se orgulhou das minhas conquistas, obrigada por sempre ter feito tudo para o nosso melhor. À minha irmã, obrigada por sempre me ouvir, por ter dividido a vida comigo, pela lealdade e por saber que sempre poderei contar contigo.

Meu companheiro Maicon, obrigada por acreditar mais em mim do que eu mesma, por toda paciência durante esses anos, por todo colo e carinho. Meus agradecimentos nunca serão suficientes. À minha filha canina Branca, por estar sempre ao meu lado e por todos os momentos de distração e alegrias que me proporcionou.

À tia Sandra, minha segunda mãe, obrigada por me tratar como uma filha, obrigada por sempre me auxiliar nos momentos que precisei, com certeza não teria sido possível sem ti. À minha afilhada Alice, obrigada por entender todas as minhas ausências e por sempre acreditar na tua dinda!

Aos meus amigos, poucos e bons, obrigada pelo apoio desde o início dessa jornada, por sempre falarem com orgulho de mim, por escutarem minhas angústias em todos esses anos, por me incentivarem e por sempre estarem ao meu lado: David, Vinícius, Ana e Ruth, obrigada!

As amigas que construí durante estes anos de graduação, obrigada por dividirem comigo as dúvidas, anseios, aprendizados e momentos incríveis durante nosso curso, com certeza não seria igual se não tivesse vocês comigo: Ana, Bárbara e Fran.

Aos colegas e amigos do grupo de pesquisa Wound Healing Research Group (WHOC) ou famosos “manoeletes’’, agradeço pelas oportunidades de aprender com cada um de vocês, sem dúvida foi uma das melhores partes da graduação; em especial a Tuany e Jéssica que dividiram meus primeiros momentos na iniciação científica, e Laura, Lauren e Felipe pelos momentos finais.

À Marina Curra, todo este trabalho não existiria sem ti, obrigada por me acolher, por me ensinar tanto e pelos momentos que passamos juntas no 3° leste, sou grata e te admiro muito!

À minha orientadora Manoela, palavras não são suficientes para te agradecer. Acredito que nosso encontro foi especial, ter uma orientadora, amiga, mãe científica e conselheira é para poucos. Obrigada por todas as oportunidades que tu me deste, por ser minha guia e inspiração. Seguimos juntas.

À faculdade de Odontologia da UFRGS pela oportunidade de ter concluído este curso. Ao CNPq, ao Capes, a Fapergs e ao PRONON por todo fomento durante estes anos de iniciação científica.

Por fim a Universidade Federal do Rio Grande do Sul (UFRGS) pela oportunidade de cursar um ensino público e de qualidade.

Se as coisas são inatingíveis... ora!

Não é motivo para não querê-las...

Que tristes os caminhos, se não fora

A presença distante das estrelas! (Mário Quintana)

RESUMO

A mucosite oral (MO) é uma reação tóxica, aguda e inflamatória causada pelos regimes citotóxicos para o tratamento de diferentes neoplasias. Apesar da MO afetar grande parte dos pacientes que recebem tratamento antineoplásico, nem todos os pacientes desenvolvem a forma grave da MO, a importância de identificar quais fatores de risco podem levar ao desenvolvimento de quadros graves da MO, auxilia no correto manejo e intervenção em cada caso individualmente. Em crianças, poucos estudos relatam os fatores de risco associados a MO e as individualidades desta população devem ser consideradas. No presente trabalho de conclusão de curso realizamos 3 estudos nesta temática. No artigo 1 realizamos uma revisão sistemática com o objetivo de identificar potenciais fatores de risco associados ao desenvolvimento de OM em pacientes pediátricos com câncer. Uma busca foi realizada em quatro bases de dados eletrônicas para identificar estudos que analisaram os fatores de risco para OM em pacientes pediátricos com câncer. Dezenove artigos foram incluídos. A incidência de OM variou de 20% a 80,4%. Os agentes quimioterápicos foram fatores de risco potenciais para MO em oito (42%) estudos. Parâmetros hematológicos, hepáticos e renais também foram considerados em oito (42%) estudos, enquanto fatores individuais específicos foram relatados em cinco (26,3%) estudos. Doença de linha de base, microbiota oral, perfil genético e biomarcadores foram relatados em quatro (21,5%) estudos cada. Meta-análise mostrou que os grupos submetidos a alto risco quimioterapia para OM teve um aumento de 2,79 vezes aumento do risco de OM. No artigo 2 objetivamos avaliar a relação do MO com o tempo de metabolismo do metotrexato (MTX) e outras toxicidades em pacientes oncológicos pediátricos recebendo altas doses de metotrexato (HD-MTX). Foram avaliados setenta e sete pacientes infantis recebendo altas doses de metotrexato (HD-MTX) para tratamento de leucemia, osteossarcoma ou linfoma e a avaliação do nível sérico de MTX, hepático e parâmetros de função renal, e presença e intensidade de MO foram analisados. Os pacientes foram submetidos a 255 ciclos de quimioterapia. MO foi diagnosticada em 191 (74,9%) ciclos. Destes, 119 (46,6%) apresentaram lesões ulcerosas. O linfoma foi associado a MO grave (p= 0,01). MO foi associada com níveis séricos mais elevados de aspartato aminotransferase (p= 0,006), alanina aminotransferase (p= 0,04) e creatinina (p= 0,008). O aumento de uma unidade de bilirrubina total e bilirrubina indireta foi associada, respectivamente, com 11% e 39% maior prevalência de MO. Para cada aumento de uma unidade do nível sérico de creatinina, foi observada uma prevalência 37% maior de MO em pacientes com linfoma. Nenhuma associação foi encontrada

entre a excreção retardada de MTX e o desenvolvimento de MO. No artigo 3 nosso objetivo foi investigar a incidência e os fatores de risco para mucosite oral (MO) em pacientes com câncer infantil recebendo tratamento quimioterápico. Foram avaliados oitocentos e vinte e nove ciclos de quimioterapia em 112 pacientes com câncer infantil. O protocolo de quimioterapia, parâmetros hematológicos, hepáticos e de função renal foram coletados e comparados à presença e gravidade de MO. Maior incidência e gravidade de MO foi observada em pacientes que utilizaram metotrexato em altas doses (MTX-HD), combinação de ciclofosfamida/doxorrubicina MTX-HD, e MTX-HD combinado com ciclofosfamida ($p < 0,001$). Pacientes com MO grave tinham níveis mais baixos de leucócitos ($p = 0,003$), hemoglobina ($p = 0,005$), plaquetas ($p = 0,034$) e níveis mais elevados de bilirrubina total ($p = 0,027$), alanina aminotransferase (ALT) ($p = 0,001$) e creatinina ($p = 0,007$). Estes estudos contribuíram para a elucidação dos fatores de risco para o desenvolvimento e gravidade da MO em pacientes pediátricos. Identificar precocemente estes fatores de risco é primordial para permitir um tratamento individualizado.

Palavras-chave: Mucosite oral; Oncologia; Pediatria; Fatores de risco.

ABSTRACT

Oral mucositis (OM) is a toxic, acute and inflammatory reaction caused by cytotoxic regimens for the treatment of different neoplasms. Although OM affects most patients who receive antineoplastic treatment, not all patients develop the severe form of OM, the importance of identifying which risk factors can lead to the development of severe OM conditions helps in the correct management and intervention in each case individually. In children, few studies report the risk factors associated with OM and the individualities of this population should be considered. In this undergraduate thesis we carried out 3 studies on this topic. In article 1 we perform **a** systematic review with the aim of identifying potential risk factors associated with the development of OM in pediatric cancer patients. A search was performed in four electronic databases to identify studies that analyzed risk factors for OM in pediatric cancer patients. Nineteen articles were included. The incidence of OM ranged from 20% to 80.4%. Chemotherapeutic agents were potential risk factors for OM in eight (42%) studies. Hematological, hepatic, and renal parameters were also considered in eight (42%) studies, while specific individual factors were reported in five (26.3%) studies. Baseline disease, oral microbiota, genetic profile, and biomarkers were reported in four (21.5%) studies each. Meta-analysis showed that groups undergoing high-risk chemotherapy for OM had a 2.79-fold increased risk of OM. In the article 2 we evaluated the relationship of OM with methotrexate metabolism time (MTX) and other toxicities in pediatric cancer patients receiving high doses of methotrexate (HD-MTX). Seventy-seven pediatric patients receiving high doses of methotrexate (HD-MTX) for the treatment of leukemia, osteosarcoma or lymphoma were evaluated and the assessment of serum MTX level, liver and renal function parameters, and the presence and intensity of OM were analyzed. Patients underwent 255 cycles of chemotherapy. OM was diagnosed in 191 (74.9%) cycles. Of these, 119 (46.6%) had ulcerous lesions. Lymphoma was associated with severe OM (p= 0.01). OM was associated with higher serum levels of aspartate aminotransferase (p= 0.006), alanine aminotransferase (p= 0.04) and creatinine (p= 0.008). An increase of one unit of total bilirubin and indirect bilirubin was associated, respectively, with 11% and 39% higher prevalence of OM. For every one-unit increase in serum creatinine level, a 37% higher prevalence of OM was observed in patients with lymphoma. No association was found between delayed MTX excretion and OM development. In article 3 we investigated the incidence and risk factors for oral mucositis (OM) in childhood cancer patients receiving chemotherapy treatment. Eight hundred twenty-nine cycles of chemotherapy were evaluated in 112 patients with childhood cancer. Chemotherapy

protocol, hematological, hepatic, and renal function parameters were collected and compared to the presence and severity of OM. Higher incidence and severity of OM was observed in patients who used high-dose methotrexate (MTX-HD), cyclophosphamide/doxorubicin combination, MTX-HD, and MTX-HD combined with cyclophosphamide ($p<0.001$). Patients with severe OM had lower levels of leukocytes ($p= 0.003$), hemoglobin ($p= 0.005$), platelets ($p= 0.034$) and higher levels of total bilirubin ($p= 0.027$), alanine aminotransferase (ALT) ($p= 0.001$) and creatinine ($p= 0.007$). These studies contributed to the elucidation of risk factors for the development and severity of OM in pediatric patients. Early identification of these risk factors is essential to allow an individualized treatment.

Keywords: Oral mucositis; Oncology; Pediatric; Risk Factors.

SUMÁRIO

1. ANTECEDENTES E JUSTIFICATIVA

O câncer causa uma morbidade e mortalidade grande na população infantil, apesar da sobrevida em 5 anos ter aumentado em grande parte dos países desenvolvidos, alguns diagnósticos ocorrem tardiamente, especialmente na população de baixa renda, o que pode agravar o prognóstico destes pacientes. Estimou-se 397.000 casos incidentes de câncer infantil em todo o mundo em 2015, destes apenas 224.000 foram diagnosticados, 43% dos casos de câncer infantil no mundo foram subnotificados. Alguns fatores individuais importantes para o prognóstico de pacientes infantis incluem idade, sexo, o tipo da neoplasia, o estágio, o local acometido e outros fatores clínicos durante o diagnóstico (1-4). A quimioterapia tem sido utilizada na população infantil desde 1950, entretanto a toxicidade era tanta que os pacientes morriam devido ao uso dos quimioterápicos, o avanço científico das combinações dos protocolos quimioterápicos aumentaram a sobrevivência e as toxicidades diminuem substancialmente, entretanto nos tratamentos para essas neoplasias os efeitos colaterais e toxicidades dos agentes quimioterápicos ainda ocorrem, a relação da eficácia do medicamento e da sua toxicidade são muito próximas. Atualmente, identificar para quais pacientes o uso dos quimioterápicos pode ser mais intenso sem comprometer a sobrevivência tem sido o objetivo dos protocolos mais recentes (4, 5). As toxicidades resultantes do uso de diferentes quimioterápicos e combinações podem causar citotoxicidade da medula óssea causando neutropenia, anemia e trombocitopenia. Lesões cardíacas também podem ocorrer causada por algumas classes de quimioterápicos, além de náuseas e vômitos que representam efeitos colaterais comuns induzidos pela quimioterapia. A mucosite oral (MO) é uma toxicidade muito frequente em pacientes que utilizam quimioterápicos para o tratamento antineoplásico (5-10).

MO é uma reação tóxica, aguda e inflamatória causada pelos regimes citotóxicos (quimioterápicos e/ou radioterapia de cabeça e pescoço) para o tratamento de diferentes neoplasias. A MO é caracterizada pelo desenvolvimento de lesões ulceradas e profundas que geram dor aos pacientes, os tecidos menos queratinizados são mais afetados e as lesões se apresentam como áreas eritematosas ou esbranquiçadas, ou ulceradas. Desde a infusão do quimioterápico, a nível celular a MO começa a progredir e a partir do 4° dia as lesões se instalam clinicamente, durando cerca de 10 dias até sua cicatrização completa (11). As lesões de MO dificultam a alimentação dos pacientes, necessitando de suporte alimentar para nutrição, além disso, sítios para infecções secundárias ocorrem em lesões ulceradas e expostas na cavidade oral, há uma diminuição na qualidade de vida dos pacientes com MO durante o curso do tratamento e os custos efetivos de pacientes com MO em graus severos é elevado, além disso,

ocorre um aumento do uso de medicamentos opioides e do tempo de internação hospitalar destes pacientes; a interrupção do tratamento antineoplásico pode ocorrer devido a gravidade destas lesões (12-15). Por causar tantas complicações, a prevenção e tratamento da MO vem sendo amplamente estudada. Protocolos de higiene bucal são de extrema importância para manter a cavidade oral sem sítios de infecção e inflamação, a crioterapia oral, o uso de medicamentos como anestésicos tópicos, anti-inflamatórios, antifúngicos, barreiras mucosas, agentes de revestimento e citoprotetores tem sido bem utilizado, além disso, a fotobiomodulação é descrita como fator imprescindível na prevenção e tratamento da MO (16-20).

Apesar da MO afetar grande parte dos pacientes que recebem tratamento antineoplásico nem todos os pacientes desenvolvem a forma grave da MO, divergências na forma como a MO se manifesta em diferentes pacientes, pode ocorrer devido a individualidades ou até mesmo fatores específicos genéticos. A importância de estudos que possam identificar quais são estes fatores, considerados de risco para o desenvolvimento de quadros graves da MO, podem levar a abordagens personalizadas e auxiliar no correto manejo destas lesões. Estes fatores que podem levar a diferentes graus de desenvolvimento da MO têm sido discutidos e descritos na literatura, especialmente na população adulta. Estudos descrevem como fatores de risco para a ocorrência de MO os agentes quimioterápicos, as variantes em genes específicos relacionados à codificação de enzimas importantes associadas ao metabolismo e transporte dos agentes quimioterápicos, à microflora oral, à sinalização imunológica e os mecanismos de lesão celular (21-24). Além disso, outras toxicidades importantes, como hematológicas, renais e hepáticas, podem ser observadas em concomitância com o desenvolvimento e severidade da MO (25-27).

A população infantil apresenta peculiaridades no que diz respeito ao tratamento antineoplásico utilizado, a resposta biológica e a outros fatores individuais nesta população; poucos estudos da literatura relatam potenciais fatores de risco para o desenvolvimento e severidade da MO em pacientes pediátricos. Neste sentido, o objetivo destes estudos foi identificar os potenciais fatores de risco para o desenvolvimento e severidade da MO, incidência de MO e a relação com outras toxicidades em pacientes oncológicos pediátricos para desenvolver um melhor manejo e individualização do tratamento.

2. ARTIGO CIENTÍFICO - 1

Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta-analysis

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Este trabalho de conclusão de curso foi publicado na revista Oral Diseases; 2021.

de Farias Gabriel A, Silveira FM, Curra M, Schuch LF, Wagner VP, Martins MAT, da Silveira Matte U, Siebert M, Botton MR, Brunetto AT, Gregianin LJ, Martins MD.Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta-analysis.Oral Dis. 2021 Mar 28. doi: 10.1111/odi.13863. Online ahead of print.PMID: 33774891 Review. IF: 3.511 QualisA2

Received: 30 January 2021 | Revised: 2 March 2021 | Accepted: 25 March 2021

DOI: 10.1111/odi.13863

REVIEW ARTICLE

ORAL DISEASES WILEY

Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta-analysis

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Funding information
PRONON/Ministry of Health, Brazil, Grant/Award Number: 25000.056.976/2015-52; Postgraduate Research Group of Porto Alegre Clinics Hospital, Grant/Award Number: 2016-0608; Brazilian National Council for Scientific and Technological Development; Children's Cancer Institute; Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior-Brazil, Grant/Award Number: 001; CNPq

Abstract

Objectives: Oral mucositis (OM) is an acute toxicity related to cancer treatment. This systematic review aimed to identify potential risk factors associated with the development of OM in pediatric cancer patients.

Methods: A search was performed in four electronic databases to identify studies that analyzed risk factors for OM in pediatric cancer patients.

Results: Nineteen articles were included. The incidence of OM ranged from 20% to 80.4%. Chemotherapeutic agents were potential risk factors for OM in eight (42%) studies. Hematological, hepatic, and renal parameters were also considered in eight (42%) studies, while specific individual factors were reported in five (26.3%) studies. Baseline disease, oral microbiota, genetic profile, and biomarkers were reported in four (21.5%) studies each. Meta-analysis showed that groups submitted to high-risk chemotherapy for OM had a 2.79-fold increased risk of OM.

Conclusions: Identifying risk factors for OM is essential in order to allow individualized and early prevention treatment.

KEYWORDS
childhood cancer, oral mucositis, oromucositis, pediatric cancer, risk factors

1 | INTRODUCTION

Cancer represents the second leading cause of death in the pediatric population and about 13.7 million new cases of cancer are estimated to occur in children worldwide between 2020 and 2050 (Atun et al., 2020). The main treatment modalities for cancer include surgery, radiotherapy (RT), and/or chemotherapy (CT). Although CT is a widely used and effective method for the treatment of cancer, it may be highly toxic for all rapidly dividing cells such as the ones from the oral mucosa (Maranhão et al., 2017; Meeske et al., 2020). In this context, oral mucositis (OM) represents a common acute toxicity related to the antineoplastic agents. OM is characterized by an inflammatory reaction clinically presenting as erythematous and/or ulcerated lesions with a preference for the regions of buccal mucosa, dorsal tongue, floor of the mouth, and soft palate. The keratinized mucosa is less affected (Villa & Sonis, 2020). The initial lesions are generally an erythema that may progress to erosive and/or ulcerated lesions (Hurrell et al., 2019; Lalla et al., 2014; Sonis, 2009; Villa & Sonis, 2020).

The pathogenesis of OM involves multiple phases and different complex biological processes. The Initiation stage occurs after the damage caused by antineoplastic agents to the DNA of the cells, which ultimately generates reactive oxygen species (ROS). The message generation phase in response to the initiation phase triggers a cascade of biological and immunological events, causing cell apoptosis and also damaging connective tissue. In the signal amplification phase, different signaling pathways are activated by pro-inflammatory cytokines, consequently causing clinical erythema and edema in the oral mucosa. Due to the damaged oral epithelial cells, the process progresses to the ulceration phase. Finally, an increase in cell proliferation and migration is stimulated, ultimately leading to the event of mucosal healing (Bockel et al., 2018; Sonis, 2004, 2011).

The frequency of OM may range from 51.7% to 75% in patients receiving CT (Çakmak & Nural, 2018; Mazhari et al., 2019), and from 73% to 90% in those undergoing hematopoietic stem cell transplantation (HSCT) (Chaudhry et al., 2015; Vitale et al., 2017). OM may impair oral feeding and increase the risk of secondary and opportunistic infections, causes delays or interruptions of antineoplastic therapy, increases the use of opioid drugs, hospital stay, and treatment costs, and affects the quality of life of the patient (Bezinelli et al., 2014; Martins et al., 2019). Different therapeutic approaches may be used for both the prevention and treatment of OM, including oral care protocols, cryotherapy, herbal medicines, anti-inflammatory drugs, growth factors, cytokines, and photobiomodulation therapy (PBMT) (He et al., 2018; Lauritano et al., 2014; Mazhari et al., 2019; Zadik et al., 2019).

Since not all patients will develop OM, identifying key risk factors that can predict the course of this condition is vital, by permitting clinicians to design personalized therapies. Some risk factors associated with OM development and severity has already been described in the adult and pediatric population. In adults, OM risk is associated with the chemotherapeutic regimen, the variants in specific genes related to the encoding of important proteins associated with the metabolism and transport of the chemotherapeutic agents, the oral microflora, the immune signaling, and the cell injury mechanisms (Heil, 2019; Hong et al., 2019; Howard et al., 2016; Reyes-Gibby et al., 2017; Wardill et al., 2020). In children, evidence is dispersed and particularities associated with this population need to be taken into account. To the best of our knowledge, no systematic review exploring risk factors for OM in the pediatric population is currently available. In this respect, the objective of this systematic review was to identify the potential risk factors associated with the development of OM in pediatric patients.

2 | MATERIALS AND METHODS

2.1 | Protocol registration and focused question

This review was registered with the National Institute for Health Research, International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020205354). According to Preferred Reporting Items for Systematic reviews (PRISMA) guidelines (Moher et al., 2009), the following specific question was framed for this systematic review: "What are the risk factors associated with the development of OM in pediatric oncology patients?"

2.2 | Search strategy

The search strategy was based on the Populations, Interventions, Comparison, Outcomes and Study Design (PICOS) principle. Individual search strategies were designed for the following electronic databases: MEDLINE/PubMed, EMBASE, Web of Science, and Scopus. Only publications in the English language were considered, with no restrictions regarding year of publication. The search strategy contained a combination of controlled predefined Medical Subject Heading (MeSH) terms and free terms using the Boolean operators (i.e., OR and AND), always adapted to the rules of syntax of each bibliographic database. The following search strategy was constructed: ((("risk factors" OR "Factor, Risk" OR "Factors, Risk" OR "Risk Factor") AND (Child OR Pediatrics OR Pediatric OR pediatric OR infant)) AND (Neoplasms OR Neoplasia OR Neoplasias OR Neoplasm OR Tumor OR Malignancy OR Malignancies OR Cancer)) AND (Stomatitis OR "oral mucositis" OR Stomatitides OR Oromucositis OR Oromucositides OR mucositis OR mucositides). Additionally, a manual search was also performed in the reference lists of the included studies in order to locate any potentially unidentified study.

2.3 | Eligibility criteria

2.3.1 | Inclusion criteria

The present systematic review was based on original studies evaluating the risk factors associated with the development of OM in

pediatric oncology patients. The population was defined as patients ranging in age from 0 to 19 years submitted to different antineoplastic therapy protocols for the treatment of different baseline diseases.

2.3.2 | Exclusion criteria

Review papers, letters to the editor, monographs, conference papers, book chapters, unpublished data, and animal studies were excluded. In addition, the studies selected according to the search strategy were also excluded if at least one of the following points was observed: (a) the study did not demonstrate the risk factors associated with the development of OM in the evaluated patients; (b) the patients had been submitted to previous head and neck radiotherapy; and (c) the primary endpoint was not OM.

2.4 | Study selection and data extraction

The titles and abstracts of all studies obtained with the search strategy were reviewed. Initially, we selected the studies that met the inclusion criteria based on their titles and abstracts. Irrelevant studies that clearly failed the inclusion criteria were excluded and the papers finally included were read in full. The search was carried out until September 2020. Three reviewers (A.F.G.; F.M.S.; L.F.S.) conducted the research process independently and discussed with the fourth

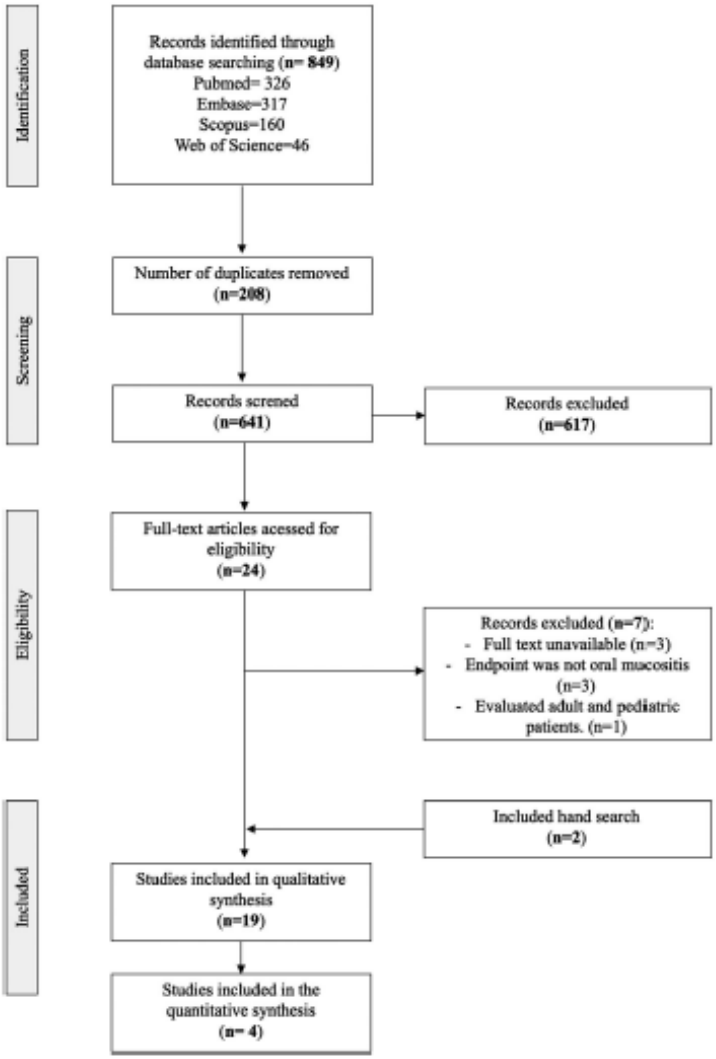

FIGURE 1 Flow chart of study selection

TABLE 1 General features of the included studies

Author (year)	Country	Study design	Population sample	Population age (mean ± SD)
Fadda et al. (2006)	Italy	RCC	337 patients	7.6 ± 5.4 (1) 7.5 ± 5.6 (2)
Gandemer et al. (2007)	France	MRT	145 patients	12.2 (5.2–18.7)
Cheng et al. (2008)	China	RCC	102 patients	7.6 ± 5.2
Cheng (2008)	China	CC	28 patients	6–17 ± 14
Figliolia et al. (2008)	Brazil	RC	169 patients	5 months–18 years
Cheng et al. (2011)	China	PC	140 patients	11.8 ± 3.3
Otmani et al. (2011)	Morocco	PC	970 patients	6.8 ± 4.1
Ozdemir et al. (2012)	Turkey	RCC	189 patients	7.09 ± 3.84
Bektaş-Kayhan et al. (2012)	Turkey	CC	115 patients	8.68 ± 4.90 10.14 ± 3.86
Ye et al. (2013)	Italy	PC	104 patients	6.6
De Faria et al. (2014)	Brazil	CS	92 patients	6 (range 2–10)
Ip et al. (2014)	China	PC	140 patients	11.8
De Mendonça et al. (2015)	Brazil	PC	71 patients	93.8 ± 65.1 months
Den Hoed et al. (2015)	Netherlands	PC	134 patients	5.3 (range 1.4–18.1)
Righini-Grunder et al. (2015)	Canada	PC	48 patients	8.3 (1–14) 8.8 (2–12)

Population sex	Type of cancer	Chemotherapeutics regimen
213 boys (63.2%) 124 girls (36.8%)	HM: HL, NH and miscellaneous ST: Osteosarcoma, Ewing's sarcoma, and rhabdomyosarcoma CT; neuroblastoma, nephroblastoma and retinoblastoma	Melphalan, Busulfan, other alkylant drug
93 boys (64%) 52 girls (36%)	HM: ALL, AML, BL, HL, Large-cell anaplastic lymphoma, T- lymphoblastic lymphoma ST: Osteosarcoma, Ewing sarcoma, Rhabdomyosarcoma and others	COPADM, VIDE, R3, B2, B3, MMT983, VANDA, Cisplatinum-doxorubicin, amustine-etoposide-cytarabine-melphalan. Second consolidation: cytarabine-etoposide-daunorubicin, high-dose etoposide, methotrexate, cyclophosphamide, doxorubicin, vinblastine, dexamethasone, methotrexate-cyclophosphamide, doxorubicin- dexamethasone, weekly high-dose methotrexate (12 g/m^2), ifosfamide-vincristine-etoposide, misulban-melphalan
65 boys (63.73%) 37 girls (36,27%)	HM: ALL, AML ST: Osteosarcoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma	Plant alkaloids (vincristine and etoposide), antitumor antibiotics (daunorubicin), alkylating agent (cyclophosphamide and melphalan), antimetabolites (Ara-C and MTX)
18 boys (64.2%) 10 girls (35.7%)	ALL and osteosarcoma	HD-MTX: 5–12 g/m^2
59.2% boys 40.8% girls	ALL	BCLSG-93, ALL-BFM-95, BCLSG-99, ALL-BFM-02
88 boys (63%) 52 girls (37.1%)	HM and ST	Etoposide; MTX; adriamycin; combined etoposide, ara-C and/or adriamycin
619 boys (63.8%) 351 girls (36.2%)	HM: ALL, NHL, HL ST: Renal tumors, Neuroblastoma, Bone tumors, Soft tissue sarcoma, Retinoblastoma, UCNT, Hepatic tumors, Teratoma	Cisplatin, carboplatin, VCR, daunorubicin, doxorubicin, MTX, ara-C, etoposide, Ifosfamide, bleomycin, actinomycin, 6-mercaptopurine, vinblastine, asparaginase
62 boys (69%) 28 girls (31%) cases 55 boys (56%) 44 girls (44%) control	ALL and BL	BFM-B cell NHL-95; Modified ALL-BFM 90 protocol and BFM-TR ALL 2000
34 boys (72.3%) 13 girls (27.7%) cases 43 boys (63.2%) 25 girls (36.7%) control	ALL	NI
66 boys (63%) 38 girls (37%)	HM: ALL, AML, NHL, HL ST: Brain tumor, renal tumor, soft tissue sarcoma, skeletal sarcoma, retinoblastoma, neuroblastoma, hepatoblastoma, pleuropulmonary blastoma, nasopharyngeal carcinoma	MTX, doxorubicin, Ara-C, cyclophosphamide, actinomycin, cisplatin, etoposide
53.3% boys 46.7% girls	ALL	MTX
88 boys (62.9%) 52 girls (37.1%)	HM and ST	Etoposide, MTX, ara-C, adriamycin, anthracycline, etoposide, cytarabine and/or adriamycin
44 boys (61.9%) 27 girls (38.1%)	ALL	VCR, doxorubicin, asparaginase, MTX, Ara-C
70 boys (52%) 64 girls (47%)	ALL	HD-MTX
HSV1 Negative boys (70.6%) girls (29.4%) HSV1 Positive boys (85.7%) girls (14.2%)	HM: ALL, AML, NHL, HL ST: Osteosarcoma, Ewing's sarcoma, Langerhans cell histiocytosis, Rhabdomyosarcoma, Malignant Rhabdoid Tumor	NI

TABLE 1 (Continued)

Author (year)	Country	Study design	Population sample	Population age (mean ± SD)
Allen et al. (2017)	Australia	PC	73 patients	NI
Ribeiro et al. (2019)	Brazil	PC	105 patients	7.30 ± 5.17
Damascena et al. (2020)	Brazil	RC	142 patients	NI
Valer et al. (2020)	Brazil	RC	77 patients	8.36 ± 4.88

Note: Abbreviations: ALL, Acute lymphoid leukemia; AML, Acute Myeloid Leukemia; Ara-C, Cytarabine; BL, Burkitt lymphoma; CNS, Central Nervous System; CS, Cross, sectional; CT, Cerebral tumors; HD-MTX, High-dose methotrexate; HL, Hodgkin's Lymphoma; HM, Hematological malignancies; MRT, Multicenter randomized trial; MTX, Methotrexate; NHL, Non-Hodgkin's Lymphoma; PC, Prospective cohort; PCC, Prospective case-control; RC, Retrospective cohort; RCC, Retrospective case-control; ST, Solid Tumors; UCNT, Undifferentiated nasopharyngeal cancer; VCR, vincristine.

COPADM - cyclophosphamide, vincristine, prednisone, MTX (3 g/m^2 and 8 g/m^2), doxorubicin; VIDE - : vincristine, ifosfamide, doxorubicin, etoposide, misulban, melphalan, cisplatin, doxorubicin; R3 - VCR, etoposide, cytarabine, dexamethasone; B2 - Thioguanine, vindesine, MTX, cyclophosphamide, amacrine-L asparaginase; B3- Ara-c, etoposide-L asparaginase, dexamethasone, cytarabine, etoposide, daunorubicin; MMT98 3 - High-dose etoposide; VANDA-cytarabine, mitoxantrone, etoposide-L asparaginase, dexamethasone, MTX, cyclophosphamide, doxorubicin, vinblastine, dexamethasone HD- MTX (12 g/m^2), Ifosfamide, vincristine, etoposide; ALL-BFM-02 - vincristine, Daunorubicin, MTX, mercaptopurine, cyclophosphamide, Ara-c, doxorubicin, tioguanine, etoposide; BFM-B cell NHL-95 - Cyclophosphamide, MTX; COG AHOD0031- doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide e prednisone (ABVE-PC) dexamethasone, etoposide, cisplatin e cytarabine (DECA); AHOD0831 - ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), phosphamide/vinorelbine. ALL-BFM 95 – Vincristine, daunorubicin, methotrexate, Ara-c, 6-mercaptopurine, Ifosfamide, Etoposide, Doxorubicin, Cyclophosphamide, 6-thioguanine.

one (M.D.M.) when disagreement occurred. The required information from the eligible studies was collected by one of the reviewers (A.F.G.). For each study, the following data were extracted using a standardized data collection form: (a) publication details (first author, year and country); (b) study design; (c) population sample; (d) population age; (e) population sex; (f) type of cancer; (g) chemotherapy regimen; (h) incidence of OM; *and* (i) OM-associated risk factors. All data extracted were inserted into a database using EndNote software (Thompson Reuters).

2.5 | Risk of bias assessment

The critical evaluation of the included articles was carried out based on the Joanna Briggs Institute – University of Adelaide – JBI Manual for Evidence Synthesis (Moola et al., 2020). The included articles were evaluated according to the parameters of each type of study: cohort, case–control, cross-sectional, and randomized studies. For each parameter, the included article was classified as "yes", "no" or "unclear".

2.6 | Synthesis of the results

A meta-analysis was conducted on the included studies that showed methodological homogeneity. The Review Manager version 5.3 software (RevMan) [Computer program], version 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) was used. Statistical heterogeneity was assessed by means of the I^2 statistics. The random model was deployed (Higgins & Thompson, 2002) due to high heterogeneity.

3 | RESULTS

3.1 | Study selection

The flowchart in Figure 1 shows the review process and the selection of the included studies. The search strategy in the electronic databases resulted in 849 articles. After removing 208 duplicates, the eligibility criteria were applied to 641 references and 24 articles were selected for full-text reading. Seventeen articles were finally included

Population sex	Type of cancer	Chemotherapeutics regimen
NI	HM: ALL, AML, HL, NHL ST and CNS	COG AHOD0031, COG AHOD0831, AEIOP-BFM ALL 2009 IntReALL 2010 SR, R3 Relapsed ALL Trial, COG AAML1031, COG AAML0531, APML4, COG ANHL1131 LCHIV, COG ALCL99, COG AOST0331, COG AHEP0731, COG ANBL0531, COG AREN0321, COG AEWS1031, COG ACNS0332 COG ACNS0334, SIOP LGG2003
57 boys (54.3%) 48 girls (45.7%)	HM and ST	Alkylating agents (cyclophosphamide; ifosfamide), Antimetabolites (Ara C; MTX), Natural products (actinomycin D; daunorubicin; doxorubicin; VCR); miscellaneous(cisplatin)
73 boys (51.4%) 69 girls (48.6%)	HM: ALL, AML, HL, NHL ST: Wilms' tumor, osteosarcoma embryonal rhabdomyosarcoma, adenocarcinoma, neuroblastoma, brain stem tumor, bladder tumor, spinal tumor, germ cell tumor, melanoma, lymphoepithelioma, alveolar soft part sarcoma, synovial sarcoma	Alkylating agents, Antimetabolites, Natural product and miscellaneous
44 boys (57%) 33 girls (43%)	Leukemia, osteosarcoma, and lymphoma	HD-MTX (>1 g/m^2)

after detailed reading and two articles were further added by manual searching. Nineteen articles were finally included in this systematic review.

3.2 | General features of the included studies

The general characteristics of the included studies are summarized in Table 1. The studies were published between 2006 and 2020 and were conducted in the following countries: Brazil (six articles), China (four articles), Turkey (two articles), Italy (two articles), France, Canada, Morocco, Australia, and the Netherlands (one article each). The included articles were observational studies, as follows: cohort ($n = 11$), control cases ($n = 6$), cross-sectional ($n = 1$), and randomized multicenter study ($n = 1$).

The population sample of the studies ranged from 28 to 970 patients. The mean age of the patients was reported in 17 studies (weighted average 7.96), ranging from 0 months to 18 years. The sex of the patients was reported in 18 studies, with a predilection for boys in all of them. Regarding the types of cancer, acute lymphoblastic leukemia (ALL) was the only disease included in five studies, whereas the other 14 articles reported patients with different hematological neoplasms or solid tumors. Of the 19 publications included, only two did not identify which CT regimen was used for antineoplastic therapy. The other studies described different chemotherapeutic agents, all of them according to the type of neoplasm treated.

3.3 | OM assessment

The following scales for OM assessment were used in the included studies: WHO in eight studies (42.2%); the National Cancer Institute (NCI) in four studies (21.1%); the Oral Assessment Guide (OAG) in two studies (10.6%); the Mouth and Throat Soreness-Related and Mucositis Quality of Life Scale (MTS-OMQoL) in one study (5.2%); Mouth and Throat Soreness-Related Questions of the Oral Mucositis Daily Questionnaire (OMDQ MTS-C) in one study (5.2%); three articles (15.8%) did not report the OM scale measurement used. Eleven of the nineteen studies described the

TABLE 2 Risk Factors and Incidence of OM

Author (year)	OM incidence	Chemotherapeutic Agents	Underlying disease	Specific individual factors	Hematological, liver and renal parameters	Genetic profile and biomarkers factors	Oral microbiota
Fadda et al. (2006)	Nil	Busulfan	Germinal tumors	–	–		Secondary bacterial infections
Gandemer et al. (2007)	69%–79%	COPADM VIDE and multidrug conditioning regimens[a]	---	---	–		
Cheng et al. (2008)	Nil	---	---	Lower body weight	Higher creatinine Lower ANC Higher AST/ALT[b]		
Cheng (2008)	Nil	Plasma concentration p-MTX 66h ≥ 0.2 mmol/l	---	Nausea Vomiting	---		
Figliolia et al. (2008)	46%	ALL-BFM-95	---	---	---		
Cheng et al. (2011)	41%	---		Anxiety level Prior OM	Neutropenia[c]		
Otmani et al. (2011)	55.6%	MTX	Hematological malignancies (NHL, Acute leukemia) and UCNT	---	---		
Ozdemir et al. (2012)	Nil	---	---	---	---	*XRCC1* 399Gln allele for the rs25487 variant	
Bektaş-Kayhan et al. (2012)	80.4%					CT genotype of the c.3435C>T (rs1045642) variant in the *MDR1* gene	
Ye et al. (2013)	57%	–	Malignancy diagnosis		Low lymphocyte count[d]	Higher concentration of IL-6, IL-8, and IFN c; lower levels of pro-LL-37[e]	
De Faria et al. (2014)	70.7%						Virus HSV-1
Ip et al. (2014)	41%			Higher level of anxiety Previous history of OM	Neutropenia		
De Mendonça et al. (2015)	103 episodes				Low platelet count Low neutrophil count		HSV-1 Candida spp

(Continues)

TABLE 2 (Continued)

Author (year)	OM incidence	Chemotherapeutic Agents	Underlying disease	Specific individual factors	Hematological, liver and renal parameters	Genetic profile and biomarkers factors	Oral microbiota
Den Hoed et al. (2015)	20%					Rs7317112 A/A polymorphism in the ABCC4 gene	
Righini-Grunder et al. (2015)	50%			---	---		HSV-1 IgG positive
Allen et al. (2017)	42.5%	Chemotherapy block for HL[f]	Hematologic malignancies (ALL, AML, NHL)	Day 8 and 9 of chemotherapy cycle	Neutropenia		
Ribeiro et al. (2019)	NI	Chemotherapy antimetabolites (MTX; Ara-C)					
Damascena et al. (2020)	55.3%	Natural chemotherapy agents (daunorubicin, doxorubicin, vincristine, and etoposide)	—		White blood cell counts less 9,500/mm^3 Platelet count greater than 450,000/mm^3		---
Valer et al. (2020)	74.9%	—	—		Billirrubin total, Billirrubin indirect Creatinine		—

Note: Abbreviations: ALL, Acute lymphoblastic leukemia; ALT, Alanine aminotransferase; ANC, Absolute neutrophil count; Ara-C, Cytarabine; AST, Aspartate aminotransferase; CNT, Undifferentiated nasopharyngeal cancer; COPADM, cyclophosphamide, vincristine, prednisone, MTX, doxorubicin; HD-MTX, High-dose methotrexate; HL, Hodgkin Lymphoma; HSV-1, Herpesvirus simple; MTX, Methotrexate; MTX, Methotrexate; NHL, Non-Hodgkin Lymphoma; VCR, vincristine; VIDE, vincristine, ifosfamide, doxorubicin, etoposide, misulban, melphalan, cisplatin; WHO, World Health Organization.

COG AHOD0031- doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide e prednisone (ABVE-PC) dexamethasone, etoposide, cisplatin e cytarabine (DECA); COG AHOD0831 - ABVE-PC: (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), phosphamide/vinorelbine. ALL-BFM 95 – vincristine, daunorubicin, methotrexate, Ara-c, 6-mercaptopurine, Ifosfamide, Etoposide, Doxorubicin, Cyclophosphamide, 6-thioguanine.

[a]The authors do not specify which chemotherapeutics belong to the multidrug conditioning regimens.; [b]The AST/ALT became non-significant in the multivariate analysis, but the authors chose to leave the final model smoke since the p-value was quite low and its observed positive association with the risk of OM made clinical sense.; [c]WHO grade 1–2 and 3–4 neutropenia.; [d]Patients with solid tumors.; [e]Patients with acute leukemia.; [f]The chemotherapy block COG AHOD0031 and COG AHOD0831.

TABLE 3 General information about chemotherapy regimen and OM

Author (year)	Incidence OM	Chemotherapeutic agents	Description of chemotherapy agents	Grade OM (Scale)
Fadda et al. (2006)	NI	Busulfan	Busulfan	Presence of OM (NCI)
Gandemer et al. (2007)	69%–79%	COPADM VIDE	Cyclophosphamide, vincristine, prednisone, MTX (3 g/m2 and 8 g/m2), doxorubicin@@ Vincristine, ifosfamide, doxorubicin, etoposide, misulban, melphalan, cisplatin	Severe OM (WHO Grade 3–4)
Cheng (2008)	NI	MTX	p-MTX 66h ≥ 0.2 mmol/l (5–12 g/m^{2})	WHO grade ≥2 OM
Figliolia et al. (2008)	46%	ALL-BFM-95	Vincristine, daunorubicin, MTX, ara-C, 6 mercaptopurine, ifosfamide, etoposide, doxorubicin, cyclophosphamide, 6-thioguanine[a]	Presence of oral mucositis
Otmani et al. (2011)	55.6%	MTX	MTX	Severe OM (WHO Grade 3–4)
Allen et al. (2017)	42.5%	COG AHOD0031 COG AHOD0831 for HL	Doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide e prednisone (ABVE-PC), dexamethasone, etoposide, cisplatin e cytarabine (DECA); ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), phosphamide/ vinorelbine[b]	Severe OM (WHO Grade 3–4)
Ribeiro et al. (2019)	NI	Chemotherapy antimetabolites	MTX and Ara-C	Severe OM (OAG "3")
Damascena et al. (2020)	55.3%	Natural chemotherapy	Daunorubicin, doxorubicin, vincristine and etoposide	Presence of OM (OAG)

Abbreviations: Ara-C, Cytarabine; HD-MTX, High-dose methotrexate; MTX, Methotrexate; VCR, vincristine.
[a]Chemotherapeutic agents were not described in the study.; [b]Chemotherapeutic agents were not described in the study.

calibration of the researchers responsible for assessing the degrees of mucositis. Among them, three validated the calibration of their researchers using the kappa coefficient. Most studies did not describe the follow-up time considered during the assessment of OM. Finally, the included studies used different methods for assessing OM. Some of them assessed its severity, while others used a binary classification based on the presence or absence of OM. The present review analyzed the risk factors associated with the development of OM without performing a relationship with the severity of this condition.

3.4 | Incidence of and risk factors associated with OM in the pediatric patients

The incidences and the risk factors associated with OM in the included studies are described in Table 2. The reported incidence of OM ranged from 20% to 80.4%. In one study, OM incidence was reported as number of episodes and in five articles the incidence of OM was not reported.

The included studies assessed different risk factors potentially involved in the development of OM. For a better presentation in this systematic review, the risk factors were grouped into the following main categories: (a) chemotherapeutic agents; (b) underlying disease; (c) specific individual factors; (d) hematological, liver, and renal parameters; (e) genetic profile and biomarker factors; and (f) oral microbiota factors. The risk factors reported below had significant statistical validation in the studies, determined by logistic regression. The main characteristics observed in each of the risk factor categories are described below.

3.4.1 | Chemotherapeutic agents

Chemotherapeutic agents were the main risk factors reported in the present systematic review. Eight of the nineteen studies (42%) presented the chemotherapeutic agents as a potential risk factor for OM development. The identification of high doses of methotrexate (MTX) alone was presented in two studies (Gandemer et al., 2007; Cheng, 2008). In the study conducted by Cheng (2008), a plasma level of MTX66h ≥ 0.2 mmol/l was considered to be an important risk factor for the development of OM. Some specific protocols and each chemotherapeutic agent reported in these protocols for the treatment of some neoplasms are described in Table 3, such as COG AHOD0031 and COG AHOD0831 for the treatment of Hodgkin lymphoma (HL) (Allen et al., 2017), leukemias (BFM-95) (Figliolia et al., 2008), Burkitt's lymphoma, ALL and Ewing's sarcoma (COPADM, VIDE and multidrug conditioning regimen) (Gandemer

et al., 2007), which were also considered to be factors. Other agents, such as daunorubicin, doxorubicin, vincristine, and etoposide (Damascena et al., 2020), busulfan (Fadda et al., 2006), MTX, and cytarabine (Ara-C) (Ribeiro et al., 2019), were also presented as potential risk factors.

3.4.2 | Underlying disease

Four studies (21%) considered the underlying disease as a risk factor for OM. Hematological malignancies were described in two studies (Allen et al., 2017; Otmani et al., 2011), specifically ALL, Acute Myeloid Leukemia (AML), HL, and Non-Hodgkin Lymphoma (NHL). The diagnosis of malignancies such as acute leukemia, solid tumors, and lymphoma was reported in the study of Ye et al. (2013), and solid tumors such as germinal tumors (Fadda et al., 2006) and undifferentiated nasopharyngeal carcinoma (UCNT) (Otmani et al., 2011) were also considered to be risk factors for OM.

3.4.3 | Specific individual factors

The following associated specific individual factors were considered to be risk factors for OM in five studies (26.3%): low body weight (Cheng et al., 2008), nausea/vomiting (Cheng, 2008), previous OM, anxiety level (Cheng et al., 2011; Ip et al., 2014), and OM on days 8 and 9 of the chemotherapy cycles (Allen et al., 2017).

3.4.4 | Hematological, liver, and renal parameters

Eight studies (42%) described hematological, liver, and renal parameters as potential risk factors for OM. Regarding hematological parameters, neutropenia (Cheng et al., 2008; Cheng et al., 2011; Ip et al., 2014; De Mendonça et al., 2015; Allen et al., 2017), white blood cell count <9,500/mm^3 (Damascena et al., 2020), low lymphocyte count in patients with solid tumors (Ye et al., 2013), high levels of platelets mm^3 (Damascena et al., 2020), and low levels of platelets (De Mendonça et al., 2015) were considered as to be risk factors for OM. High levels of creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were associated with OM in the study by Cheng et al. (2008). Valer et al. (2020) identified that high levels of total and indirect bilirubin (BB, BI) and creatinine are also risk factors for the increase in OM.

3.4.5 | Genetic profile and biomarker factors

Four articles (21%) identified gene variants and biomarkers as predictors of OM. The human gene for multiple drug resistance 1 (*MDR1* or *ABCB1*) encodes a protein responsible for the flow of multiple chemotherapeutic agents in malignant neoplasms. The CT genotype for the c.3435C>T (rs1045642) variant in the *MDR1* gene was identified as a risk factor for OM in the study by Bektaş-Kayhan et al. (2012). Another important ABC transporter gene is ABCC4, which encodes a protein associated with resistance to multiple drugs and helps with the elimination of chemotherapeutic drugs, such as MTX. Den Hoed et al. (2015) showed that the AA genotype for the rs7317112 (c.75-23516T>C) variant in the *ABCC4* gene was associated with a higher incidence of OM. The *XRCC1* gene, a DNA repair protein, is responsible for repairing DNA damage caused by active oxygen, ionization, and alkylating agents. The rs1799782 (Arg194Trp, c.580C>T) and rs25487 (Arg399Gln, c.1196G>A) variants in the *XRCC1* gene are associated with the risk of cancer and Ozdemir et al. (2012) showed that the 399Gln allele of this gene increases the risk of severe OM. On the other hand, the 194Trp allele showed a protective effect against OM. High concentrations of pro-inflammatory cytokines (IL-6, IL-8, and IFN-c) and low levels of the protein antimicrobial pro-LL-37 in patients with acute leukemia were associated with higher OM levels in the study of Ye et al. (2013).

3.4.6 | Oral microbiota

Four studies (21%) evaluated the oral microflora as a potential risk factor for the development of OM. Positive Herpes simplex virus type 1 (HSV-1) was described as a risk factor for OM in three studies (De Mendonça et al., 2015; De Faria et al., 2014; Righini-Grunder et al., 2015). In addition, oral candida ssp. was also identified as a predictor of OM in the study of De Mendonça et al. (2015). Unspecified bacterial infections were also described as risk factors for OM in the study of Fadda et al. (2006).

3.5 | Associated risk factors reported in the included studies

Although the risk factors were presented individually according to the main categories defined in this systematic review, ten studies reported more than one category of risk factors potentially related to the development of OM (Table 2). Fadda et al. (2006) found that germinal tumors, the chemotherapeutic agent busulfan, and secondary bacterial infections were associated with an increased risk for the development of OM. Cheng et al. (2008) identified low pre-chemotherapy body weight, low neutrophil counts, high levels of ALT/AST and creatinine as the main risk factors for the development of OM. Cheng (2008) and Cheng et al. (2011) – reported that nausea, vomiting, and plasma MTX concentrations, and levels of anxiety, prior OM, and neutropenia were associated with OM, respectively. In the study of Otmani et al. (2011), hematological malignancies, UCNT, and MTX were identified as risk factors for severe OM. Ye et al. (2013) demonstrated that high concentrations of some pro-inflammatory cytokines and low plasma levels of pro-LL-37 in patients diagnosed with leukemia and low lymphocyte counts in patients with solid tumors were potential risk factors for the development OM. Ip et al. (2014) found that patients with high levels of

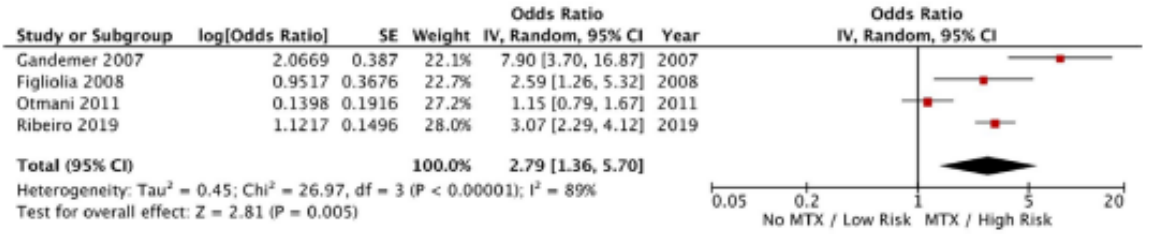

FIGURE 2 Forest plot of the risk of chances of patients receiving high-risk chemotherapy protocols that include MTX chemotherapy to develop severe grades of OM. Groups that used high-risk chemotherapy for OM showed a 2.79-fold increased risk of developing OM (of more severe grades) (95% confidence interval: 1.36–5.70). Since the studies showed significant heterogeneity ($I^2 = 89\%$, $P = p < .00001$), the random effects model was used

TABLE 4 Information about the studies included in the meta-analysis

	No/Low risk group	High doses of MTX/High risk group		
Gandemer et al. (2007)	Intermediate risk ($n = 80$)	High risk - COPADM, VIDE, and conditioning therapies ($n = 60$)	No/mild versus severe OM (WHO)	7.9 (3.7–17) (univariate)
Figliolia et al. (2008)	BCLSG-93 ($n = 65$)	ALL-BFM-95 ($n = 74$)	Absence versus presence of OM	2.59 (1.26–5.33) (Multivariate)
Otmani et al. (2011)	All other regimens ($n = 347$)	MTX ($n = 193$)	No/mild versus severe OM (WHO)	1.15 (0.79 – 1.67) (univariate)[a]
Ribeiro et al. (2019)	Alkylating agents and natural products[b]	Antimetabolites[b]	No/mild versus severe OM (WHO)	3.07 (2.29–3.85)[c]

Abbreviations: CI, confidence interval; OM, oral mucositis; OR, odds ratio.
[a]OR calculated by authors based on data extracted from the study.; [b]Sample size not available.; [c]Not informed if was univariate of multivariate analysis.

anxiety and a history of mucositis and neutropenia were more susceptible to the development of OM. De Mendonça et al. (2015) demonstrated that patients with low levels of platelets and neutrophils and patients with positive HSV-1 and candidiasis developed more OM. In the study of Allen et al. (2017), patients with hematological malignancies using specific chemotherapeutic protocols on days 8 and 9 of the CT cycles and with neutropenia developed more OM. Damascena et al. (2020) reported that patients with hematological malignancies, low white blood cell count, high platelet count and receiving a natural CT protocol had a higher risk of developing OM.

3.6 | Meta-analysis of the risk of developing severe OM after high-risk chemotherapy

A meta-analysis was conducted to compare the risk of OM according to the chemotherapeutic regimen applied. Four studies comparing groups that used high-risk chemotherapy for OM, including MTX and groups with low risk of chemotherapy for OM, without MTX, were included (Figliolia et al., 2008; Gandemer et al., 2007; Otmani et al., 2011; Ribeiro et al., 2019). The studies reported the odds ratio and 95% confidence interval or presented sufficient data for the authors to calculate these values. In three studies, the outcome was defined as OM severity (according to the WHO) and in one study, the outcome was the presence of OM. The meta-analysis showed that groups submitted to high-risk chemotherapy for OM showed a 2.79-fold increased risk of developing OM (of more severe grades) (95% confidence interval: 1.36–5.70) (Figure 2). Since the studies showed significant heterogeneity ($I^2 = 89\%$, $P = p < .00001$), the random effects model was used. Moreover, it is important to highlight that the pediatric population in each study received different chemotherapeutic agents to treat different neoplasms (Table 4). In addition, some studies did not report the correct chemotherapy doses or accurate statistical information.

3.7 | Quality assessment (risk of bias)

The risk of bias was assessed using the JBI Critical Appraisal Tools (Moola et al., 2020) for each type of observational study identified. Many studies did not identify possible confounding factors, despite having used strategies to reduce these factors, nor did they use adequate statistical analysis. In addition, few studies adjusted the analyses to remove the confounding factor from the chemotherapeutic agent (Supplementary File 1).

4 | DISCUSSION

OM is a common and debilitating inflammatory response to cancer treatment. The identification of OM risk factors can be an important tool to be used for early interventions and to facilitate personalized

support for the affected patients (Wardill et al., 2020). Recently, a robust systematic review evaluated the current evidence on the factors that influence the risk of mucositis in the general population. The study showed that the strongest level of evidence supported dosimetric parameters as an important risk factor for mucositis (Wardill et al., 2020). However, few studies have reported the potential risk factors associated with the development and severity of OM for oncological pediatric patients. By gathering all the available data in this present systematic review, we allow readers to have a more comprehensive view of the current status of knowledge concerning the risk factors for OM in this particular population. This review is valuable for clinicians in their decision-making process concerning the implementation of strategies for OM prevention by helping researchers who seek to continue exploring new risk factors or to validate the current ones in diverse oncopaediatric populations.

Nineteen studies identifying different potential risk factors for the development of OM in the pediatric population were included in this systematic review. The incidence of OM ranged from 20% to 80.4%, reflecting the heterogeneous population and the diverse methodological assessments reported in the included studies. Different combinations of chemotherapeutic agents, tumor types, patients' baseline characteristics and OM prevention protocols represent some of the variances observed. In addition, OM was evaluated using different OM scales, which may also generate some disagreement about the identification of OM degrees. The most used WHO and NCI scales are based on the score and on the ability to feed. Other scales, such as OAG, cover different categories of subjective and objective assessment. Questionnaires such as OMDQ are based on patient reports. For pediatric patients, scales that contemplate questionnaires may be complex to evaluate. There is no standard scale for pediatric patients (Tomlinson et al., 2007) and some scales may have advantages over others in the pediatric population. Standardization of OM measurement would be important when considering the comparison of the development and grade of severity of OM in different studies.

The chemotherapeutic agents represent an important risk factor for OM. For the treatment of childhood neoplasms, the chemotherapeutic agents are used at high doses, generating high toxicity (Dickens & Ahmed, 2018; Howard et al., 2016). In this systematic review, eight studies identified the chemotherapeutic agents as potential risk factors for OM. In two studies (Cheng, 2008; Otmani et al., 2011), the chemotherapeutic agent MTX alone was associated with the risk of develop OM. Cheng (2008) demonstrated that the risk of OM is associated with plasma MTX concentration at 66 hr. MTX is a chemotherapeutic agent used to treat leukemias, osteosarcomas and lymphomas, and different toxicities including OM are associated with its use (Choi et al., 2017; Park & Shin, 2016). In addition, MTX has also been described as a potential risk factor for OM in three other studies (Figliolia et al., 2008; Gandemer et al., 2007; Ribeiro et al., 2019) within protocols for the treatment of ALL, Burkitt lymphoma and Ewing's tumors. The COPADM and Vide protocols include chemotherapeutic agents other than MTX such as doxorubicin, cisplatin, cyclophosphamide, vincristine, ifosfamide, and etoposide. The ALL-BFM-95 protocol also includes agents such as vincristine, daunorubicin, ara-c, 6-mercaptopurine, ifosfamide, etoposide, doxorubicin, cyclophosphamide, and 6-thioguanine. The class of antimetabolic agents includes agents other than MTX such as Ara-c. These protocols combining two or more drugs may increase the toxic effects for the oral cavity mucosa, especially when combined with an important chemotherapeutic agent for oral toxicity like MTX. In addition, our meta-analysis showed that pediatric patients receiving protocols containing MTX had a 2.79-fold increased risk of developing OM (of more severe grades) compared to other protocols. Yet, this result needs to be interpreted with caution since there are important limitations in the analysis inherent to the heterogeneity of the studies such as primary neoplasms, drug types, and doses, and OM outcome measurement.

Allen et al. (2017) demonstrated that the chemotherapeutic protocols for the treatment of HL are potential risk factors for the development of OM. The main CT drugs included in these protocols are doxorubicin, vincristine, etoposide, cyclophosphamide, and cisplatin. The class of natural agents that includes daunorubicin, doxorubicin, and vincristine was also identified as a potential risk factor in one study (Damascena et al., 2020). The alkylating agent busulfan was a potential risk factor for the increase in OM in the study by Fadda et al. (2006). Busulfan is an important agent used in conditioning for hematopoietic cell transplantation (HCT) (Eduardo et al., 2019). Although different chemotherapeutic agents were described within the protocols used in the studies, many of these agents were combined with others, a fact that increased their toxicity. We believe that the dose of the chemotherapeutic agent as well as the combination of some chemotherapeutic agents are important risk factor to be considered.

The underlying diseases were described in four studies as potential risk factors for OM. Hematological malignances such as acute leukemia, HL, and NHL versus solid tumors were associated in three studies (Allen et al., 2017; Otmani et al., 2011; Ye et al., 2013). Two studies associated solid tumors, such as germinal tumor and UCNT (Fadda et al., 2006; Otmani et al., 2011). We believe that the potential risk factor for OM associated with the underlying disease may be more significantly related to the type of chemotherapeutic protocol used to manage the specific disease. In this respect, it was observed that three of the four studies that presented the underlying disease as a risk factor for OM also highlighted the association of the chemotherapy protocols used as risk factors for OM.

Neutropenia is also an adverse effect caused by the toxicity of chemotherapeutic agents, affecting the defense mechanisms of the immune system (Crawford et al., 2004; Lyman et al., 2014). The potential risk factors associated with hematological, liver, and renal parameters were described in eight studies in this systematic review. Although neutropenia and OM are toxicities resulting from antineoplastic treatment, most studies reported neutropenia (Cheng et al., 2008; Cheng et al., 2011; Ip et al., 2014; Allen et al., 2017) as an important risk factor for OM. Neutrophils are important agents in the inflammatory response acting in the line of defense against pathogens and their decrease may affect the body's defense process, especially during the development of OM (Kishimoto et al., 2007). The study of Damascena et al. (2020) identified that an increase in platelet count was associated with the risk of developing OM. Another factor described in the study of Ye et al. (2013) was a

low lymphocyte count at the time of diagnosis as an indicator of OM in patients with solid tumors. Factors that involve the patient's immune response may be controversial, since antineoplastic treatment causes myelosuppression, and further studies are needed to verify this relationship.

Liver toxicity represented by increased ALT and AST was reported in the study of Cheng et al. (2008). Valer et al. (2020) showed that the growth in of total BB and BI increased the prevalence of OM in pediatric patients. Unfortunately, there are few studies associating liver toxicity with OM. Higher levels of creatinine were also reported by Cheng et al. (2008) and Valer et al. (2020) as a risk factor for OM. Serum creatinine concentrations have been previously reported to delay the elimination of MTX (Xu et al., 2014). Considering that MTX is toxic to the oral mucosa cells, its delayed elimination may lead to a higher systemic concentration, potentially increasing the incidence of OM in these patients. Finally, all these risk factors involving other toxicities such as hematological, liver and renal factors described in some of the included studies may occur concomitantly with the development of OM, being a probable result of the potent chemotherapeutic agents. We understand that it is important monitoring these parameters in order to be aware of the systemic condition of the patients and because it can further help in the early identification of OM.

Changes in the genetic profile and its relationship with increased OM in pediatric patients were described in three studies. Ozdemir et al. (2012) identified that the 399Gln allele of the rs25487 variant at the *XRCC1* gene is a potential risk factor for severe OM. This repair protein has already been described in other studies as a potential risk factor for some neoplasms (Putthanachote et al., 2017). Bektaş-Kayhan et al. (2012) found that patients with the CT genotype for the c.3435C>T (rs1045642) variant of the *MDR1* gene showed an increased risk for developing OM. This gene is linked to the transport mechanism of different drugs, including chemotherapeutic drugs. The c.3435C>T variant is one of the best known for this gene and has already been studied in association with other diseases (Turgut et al., 2007; Yue et al., 2015). The identification of the heterozygous genotype for this variant may be interesting for potential investigations of patients with ALL developing OM. The *ABCC4* gene may be related to the resistance of some chemotherapy agents in some neoplasms (Drenberg et al., 2016). Den Hoed et al. (2015) reported that patients homozygous for the wild type allele (AA) of the rs7317112 variant in the *ABCC4* gene had a higher risk of developing OM.

The oral microbiota represented a potential risk factor for the development of OM in four studies included in this systematic review. Three studies highlighted HSV-1 infection as a potential risk factor. HSV-1 is a type of virus in the herpes virus family and its manifestation in infant patients is frequent. Considering the immunosuppression that occurs in cancer patients, the occurrence of HSV-1 infection may be higher in this population (Aggarwal et al., 2014; Everett, 2014). The studies described in this review suggested that patients with positive HSV-1 manifestation tended to have a more severe OM since HSV-1 can modulate the immune response and trigger severe clinical courses of OM. Secondary bacterial infection and Candida ssp. have also been described as potential risk factors for OM. Since OM generally involves the development of clinical ulcers, the diversification of oral microbiota may be potentially associated with its secondary infection. In this respect, the oral microbiota may be related to the development of OM.

While the present systematic review demonstrated important aspects regarding OM in the pediatric population, some limitations were also identified. First, the presence of different assessment scales and outcome measures for OM in the included studies impaired the execution of meta-analyses. In addition to this issue, as mentioned earlier, the present review selected the included studies based on the presentation of risk factors associated with the development of OM without performing an association with the severity of this condition. This may represent a limitation considering the existence of a possible relationship between specific risk factors and the development of a more severe grade of OM. Second, although several studies presented different potential risk factors for OM, a careful assessment of the association between these factors should be considered once they can be related to each other instead of the development of OM. Many studies describe hematological, liver, and renal complications as risk factors, but it should be interpreted with caution as they are toxicities also related to the chemoterapeutic agents. Some studies have also not reported possible confounding factors, such as the baseline characteristics of the patients, the exposure to some chemotherapeutic agents during the assessment of other risk factors, and the grading of non-standard OM. We must emphasize the importance of the correct description of the data in the statistical analyses, such as the identification of the odds ratio, the confidence interval, whether the analysis performed was univariate or multivariate, and which factors were controlled. The doses of the chemotherapy drugs considered to be risk factors were not described in all the included articles, an important omission since the doses may change according to the type of treatment. Finally, baseline pretreatment factors should be considered when assessing and describing risk factors.

Briefly, the chemotherapeutic agents are important etiological factors for the development and severity of OM lesions in pediatric cancer patients. The robust evidence in these studies demonstrates that MTX chemotherapeutic agents and its associations with other chemotherapeutic agents can be considered an important risk for the development of OM in the pediatric population. The identification of the most toxic agents for the oral cavity cells, the combinations of these different drugs, the doses used, and the eventual drug dose reduction due to the development of OM should be better described in the studies in order to allow a better understanding of their relationship with the development of toxicity. The standardization of scales for the assessment of OM has also been suggested. Scales such as the WHO (1979), which is based on patients' painful symptoms and ability to feed, and the NCI scale (Version 2.0, 1999) that assesses the appearance and size of lesions can be indicated for the assessment of OM. Conflicts between the scales may result

in different data regarding the outcome. The risk factors related to genetic diversity are other potential important factors since they evaluate individual variants within a gene that may directly interfere with the course of OM.

5 | CONCLUSION

The definition of the potential risk factors for the development of OM is important for the prevention and management of this condition, contributing to new strategies for its treatment and prevention. According to the studies included in the present systematic review, the chemotherapeutic agents (MTX and associations), the gene variants related to the course of OM and the diverse oral microbiota are points that deserve special attention when considering the risk factors for developing OM. More studies are necessary in pediatric oncological patients to standardize the assessment of risk factors and OM assessment scales.

ACKNOWLEDGMENTS

This study was supported by PRONON/Ministry of Health, Brazil (grant no. 25000.056.976/2015-52); Postgraduate Research Group of Porto Alegre Clinics Hospital (GPPG/FIPE: 2016-0608), Brazilian National Council for Scientific and Technological Development (CNPq student scholarship), Children's Cancer Institute (student scholarship), and Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior-Brazil (CAPES)-finance code 001. U.S.M. and M.D.M. are research fellows of CNPq.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Amanda de Farias Gabriel: Conceptualization; Data curation; Methodology; Writing-original draft. **Felipe Martins Silveira:** Data curation; Methodology; Writing-original draft. **Marina Curra:** Writing-review & editing. **Lauren Frenzel Schuch:** Data curation; Methodology; Writing-review & editing. **Vivian Petersen Wagner:** Data curation; Methodology; Writing-review & editing. **Marco Antonio Trevizani Martins:** Writing-review & editing. **Ursula da Silveira Matte:** Writing-review & editing. **Marina Siebert:** Writing-review & editing. **Mariana Rodrigues Botton:** Writing-review & editing. **André Tesainer Brunetto:** Writing-review & editing. **Lauro José Gregianin:** Writing-review & editing. **Manoela Domingues Martins:** Conceptualization; Supervision; Writing-review & editing.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/odi.13863.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: de Farias Gabriel A, Silveira FM, Curra M, et al. Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta-analysis. *Oral Dis*. 2021;00:1–17. https://doi.org/10.1111/odi.13863

3. ARTIGO CIENTÍFICO - 2

Oral mucositis in childhood cancer patients receiving high-dose methotrexate: Prevalence, relationship with other toxicities, and methotrexate elimination

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Este trabalho de conclusão de curso foi publicado na revista International Journal of Paediatric Dentistry
Valer JB, Curra M, Gabriel AF, Schmidt TR, Ferreira MBC, Roesler R, Evangelista JMC, Martins MAT, Gregianin L, Martins MD.Oral mucositis in childhood cancer patients receiving high-dose methotrexate: Prevalence, relationship with other toxicities and methotrexate elimination.Int J Paediatr Dent. 2021 Mar;31(2):238-246. doi: 10.1111/ipd.12718. Epub 2020 Oct 11.PMID: 32815183 IF: 3.455 QualisA1

Oral mucositis in childhood cancer patients receiving high-dose methotrexate: Prevalence, relationship with other toxicities, and methotrexate elimination

Short running title: Oral mucositis and relationship with methotrexate metabolism and toxicity

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Author contributions: J.B.V contributed on bibliographical research, data collection, data analysis and manuscript writing. M.C. conceived idea, involved on bibliographical research, design and manuscript preparation. A.F.G and T.R.S contributed to bibliographical research and data collection, M.B.C.F contributed on design and data analysis, R. R and M.C.E.J contributed to the design and critical revision of the manuscript. M.A.T.M contributed on design and data collection, L.G. involved in concepts, design and manuscript preparation and M.D.M contributed in concepts, design, data analysis, manuscript preparation and editing.

Acknowledgments: The authors are grateful to all member of Pediatric Oncology Service of Porto Alegre Clinical Hospital (HCPA/UFRGS) for support during the development of the present research.

Conflict of interests: The authors have no conflicts of interest to declare.

Funding: This study was supported by PRONON/Ministry of Health, Brazil (grant n. 25000.056.976/2015-52); Postgraduate Research Group of Porto Alegre Clinics Hospital (GPPG/FIPE: 2016-0608), Brazilian National Council for Scientific and Technological Development (CNPq student scholarship), Children's Cancer Institute (student scholarship), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brasil(CAPES)-finance code 001. Rafael Roesler and Manoela Domingues Martins are research fellow funded by the Brazilian National Council for Scientific and Technological Development (CNPq).

Word count: 3331

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Article type : Original Article

Oral mucositis in childhood cancer patients receiving high-dose methotrexate: Prevalence, relationship with other toxicities, and methotrexate elimination

ABSTRACT

Background Oral mucositis (OM) is one of the main adverse effects of the chemotherapeutic agent methotrexate (MTX).

Aim To evaluate the relationship of OM with MTX metabolism time and other toxicities in childhood, cancer patients receiving high-dose of methotrexate (HD-MTX).

Design Seventy-seven childhood patients receiving HD-MTX for treatment of leukaemia, osteosarcoma or lymphoma were evaluated. MTX serum level, *hepatic* and renal function parameters, and presence and intensity of OM were analysed.

Results The patients were submitted to 255 cycles of chemotherapy. OM was diagnosed in 191 (74.9%) cycles. Of these, 119 (46.6%) presented ulcerative lesions. Lymphoma was associated with severe OM*(p=0.01)*. OM was associated with higher serum levels of aspartate aminotransferase *(p=0.006)*, alanine aminotransferase *(p =0.04)* and creatinine (*p=0.008*). Increase of one unit of total bilirubin and indirect bilirubin associated, respectively, with 11% and 39% higher prevalence of OM. For each increase of one unit of creatinine serum level, it was observed a 37% higher prevalence of OM in patients with lymphoma. No association was found between delayed excretion of MTX and OM development.

Conclusions OM is a prevalent complication of childhood cancer patients receiving HD-MTX. Renal and hepatic toxicity could be considered risk factors for OM, especially in patients with lymphoma.

Keywords: oral mucositis, methotrexate, pediatric oncology, chemotherapy, oral toxicity

INTRODUCTION

Cancer incidence in childhood varies among countries worldwide. The overall incidence in children aged 0 to 14 years is around 40.6 per million person-years, and approximately 155.8 per million person-years in those aged 0 to 19 years, representing 2 to 3% of all cancers[1-3]. The most common types of cancer affecting these patients are leukaemias, central nerve tumours, tumours of the abdomen, lymphomas, osteosarcoma and rhabdomyosarcoma[2,3]. Despite dramatic improvements in therapeutics and early detection, cancer is still the second leading cause of infant mortality in developed countries. In Brazil, 12,500 new childhood cancer cases are diagnosed every year, with around 2,704 deaths[3]. The treatment of childhood cancer involves multimodal therapy (surgery, radiotherapy, and systemic therapy using cytotoxic agents), which has resulted in dramatic increases in survival rates. Treatment is generally adjusted for stage of disease or risk factors, with more aggressive regimens being used with advanced or metastatic disease[4].Chemotherapy protocols generally have a narrow therapeutic window, making the difference between the antitumour doses and those causing toxicity very low[5,6].

Methotrexate (MTX) has been widely used as an anticancer agent in most chemotherapy protocols for childhood cancer. MTX acts on the S phase of the cell cycle, interfering with the folic acid receptor and blocking deoxyribonucleic acid (DNA) synthesis[6-9]. Despite its clinical success, several adverse effects, and toxicities such as skin, oral, hepatic and renal toxicity continue to challenge its use in clinical practice[9-11].

Oral mucositis (OM) is considered one of the most debilitating adverse effects of chemotherapy, including MTX. Approximately 80% of childhood cancer patients experience OM to a certain extent, varying according to cancer type and treatment procedure[9,12,13]. OM represents an inflammatory reaction of the oral mucosa that clinically appears as an erythematous or painful ulcerative condition. It starts three to 10 days after the chemotherapy infusion[9]. Severe forms of OM cause shortcomings in eating and swallowing, increase rates of secondary infection and impact patients' quality of life. In addition, OM can lead to a reduction of chemotherapy dose, treatment delays, prolonged hospital stays and increased mortality[9,12]. The main risk factors for OM development include the type of treatment, previous oral health

status, age and inflammatory mediator levels. Particularly for MTX, another factor is variation in the expression of genes that encode enzymes responsible for its metabolism, transport and excretion[11,14].

Although OM is considered an important side effect of MTX treatment, the exact mechanisms involved in the development of this condition and their association with MTX metabolism is not clear in the literature. Therefore, the main aim of the present study was to evaluate the relationship of OM development with MTX metabolism time (MTX excretion) and hepatic and renal toxicity in childhood cancer patients undergoing high-dose methotrexate therapy (HD-MTX).

MATERIALS AND METHODS

The present prospective cohort study was conducted at the Paediatric Oncology Service (Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil), following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guideline for reporting cohort studies. It received approval from the Institutional Human Research Ethics Committee (HCPA protocol 16-0608 and CAEE 40921215.6.0000.5327). Patients and/or their legal guardians signed an informed consent.

Study population

It was evaluated eighty-three consecutive childhood patients (aged 0 to 18 years) receiving HD-MTX (>1 g/m²) in any chemotherapy cycle[6,15] or the treatment of leukaemia, osteosarcoma or lymphoma, between January 2015 and August 2018. Exclusion criteria comprised failure to attend a clinical evaluation of OM session, and patients with recurrent cancer. All patients received hyperhydration, bicarbonate to decrease kidney precipitation of MTX globules, and leucovorin rescue, with dose adjustment (according to MTX concentration curve, estimated every 24 hours) to reduce the development of adverse effects. All included patients received oral hygiene instructions (tooth brushing with soft brushes and rinsing with 0.12% alcohol-free chlorhexidine digluconate) prior to chemotherapy.

Procedures

Figure 1 displays the study flowchart. Demographic data (age, gender) and information about baseline disease, treatment protocol and dose and time of infusion of MTX were collected.

One cycle was characterized by the period extending from the first day of chemotherapy infusion until 15 days after the infusion. Blood samples were collected in each MTX cycle on days D1 (onset of chemotherapy), D5 (onset of immunosuppression), D10 (peak of immunosuppression), and D15 (end of chemotherapy), aiming to performed renal and hepatic analyses, including bilirubin (BB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and urea. For data analysys, it was used the highest value observed for these variables (BB, AST, ALT, urea and creatinine), in the same chemotherapy cycle. In

addition, MTX serum level (expressing the MTX excretion) was obtained 24 hours after MTX infusion, until a level of 0.2 µM, when it is no longer considered a toxic level to the organism.

Oral mucositis was evaluated daily, from D1 until D15. The World Health Organization (WHO) scale was used: grade 0 = no mucositis; grade 1 = erythema without lesions; grade 2 = ulcers, but able to eat; grade 3 = painful ulcers, but able to consume liquid food [nutrition] with analgesia for support; grade 4 = requires parenteral or enteral support and continuous analgesia. Patients who presented OM received photobiomodulation (PBM) treatment following the protocol previously described by Weissheimer et al[16].

Statistical analysis

Data are expressed as frequency, mean, standard deviation (SD), median, and 25 and 75 percentiles, according the variable analysed. Comparison of means was performed using the generalised estimated equations model. These analyses were adjusted for the dose used in each cycle and associated with the presence and severity of OM presented in the cycle. The model was composed of an independent working correlation matrix, a robust estimator covariance matrix and a gamma distribution with logarithmic binding function. When significant, the Bonferroni post hoc test was used. The clearance time analysis was performed, and its distribution was compared to the degree of OM, using the Mann–Whitney test. A Poisson regression model was used to estimate prevalence ratios and 95% CI of presence of OM (outcome), adjusted by dose. Statistical significance was obtained by the generalised linear model using Poisson distribution and evaluated by the Wald test. The analyses were performed using SPSS version 25. The significance level adopted was 0.05.

RESULTS

Patient characteristics

Eighty-three patients were included over four years of follow-up (2015–2018). Of these, six had to be excluded due to the absence of some clinical or laboratory

evaluation. Our final sample was 77 patients. Males accounted for 44 cases (57%) and females for 33 (43%), with age varying from 0 to 17 years old (8.36 ± 4.88). The diagnosed diseases were leukaemia (62.4%), osteosarcoma (19.5%) and lymphoma (18.1%; Table 1). The patients were submitted to 255 cycles of chemotherapy with MTX infusion: 113 (44.3%) were performed in leukaemia patients, 104 (40.8%) in osteosarcoma, and 38 (14.9%) in lymphoma.

All patients received HD-MTX (>1 g/m²), associated or not with other chemotherapeutic agents, according to the treatment protocol proposed for each case. Osteosarcoma patients received exclusively MTX, usually at 12 g/m². In this group, the dose of MTX was reduced in 12 patients (80%) due to side effects. In leukaemia, it was used different treatment protocols, with MTX infusion occurring in the consolidation phases, alone or associated with cyclophosphamide and doxorubicin. In lymphomas, MTX was infused concomitantly with cyclophosphamide, associated with doxorubicin or cytarabine. The mean time of MTX infusion was 17.1 hours (± 9.0) in leukaemia, 4.0 hours (± 0.0) in osteosarcoma and 8.0 hours (± 8.7) in lymphoma (Table 1).

Of the 255 cycles analysed, in 77 (30.2%), it was observed delayed elimination of MTX, taking more than 72 hours to reach a non-toxic level (0.2 µM). These comprised 30 (26.5%) of the 113 leukaemia cycles, 35 (33.6%) of the 104 osteosarcoma cycles and 13 (34.2%) of the 38 lymphoma cycles.

The analyses of renal and hepatic function were evaluated according to the base disease (Table 2). In general, patients with lymphoma showed significantly higher levels of BB, direct bilirubin(BBD), indirect bilirubin(BBI) and urea compared to other diagnosis. Patients with osteosarcoma exhibited higher levels of AST, ALT and creatinine.

Oral mucositis and methotrexate excretion analysis

OM was diagnosed in 191 (74.9%) chemotherapy cycles using MTX. Of these, 119 (46.6%) presented ulcerative lesions (grades 2, 3 and 4 on the WHO scale). Severe OM (grades 3 and 4) was observed in 39 (15.3%) cycles. OM analyses according to the disease diagnosed are shown in Table 2. Ulcerative

grades of OM were observed in 69.9% of patients with leukaemia, 77.9% of patients with osteosarcoma and 81.6% of patients with lymphoma. Severe OM (grades 3 and 4) were more observed in patients with lymphoma than in leukaemia and osteosarcoma (p=0.01; Table 3).

In all patients' cycles analysed, the excretion time of MTX (from the infusion until reaching a serum level of 0.2 µM) ranged from 48 hours to 264 hours. Table 3 shows the results of the excretion time of MTX and OM analysis. No association was found between delayed excretion of MTX and OM development (Table 4).

The relationships among OM, excretion time of MTX, and renal and hepatic function were evaluated, as shown in Table 5. No statistically significant relationship was observed between changes in hepatic and renal enzymes and the development of OM in patients with leukaemia or osteosarcoma. Patients diagnosed with lymphoma were positively associated with higher ALT, AST and creatinine values and OM development. However, when the prevalence ratio through Poisson regression was calculated, a relationship was observed between alteration in hepatic marker BB and increased chances of developing OM across the three diagnoses. An increase of one unit of total BB increased the prevalence of OM by 11%. For each increased of BI by one unit, the prevalence of OM increased by 39%. Using this model of analysis, the patients diagnosed with lymphoma should again be highlighted when relating OM with renal markers, with an increase of one unit in creatinine level elevating the prevalence of OM by 37%.

DISCUSSION

MTX is a chemotherapeutic agent routinely used to treat paediatric cancer, including leukaemia, osteosarcoma and lymphoma. MTX interferes in folic acid metabolism, and the association between HD-MTX and various side effects is well elucidated in the literature. In addition to nephrotoxicity, neurotoxicity and hepatotoxicity, OM has been the focus of many studies due to morbidity association with secondary infections, induction of parenteral nutrition, interference with planned doses, prolongation of hospitalisation and worsening quality of life[6,9,14]. However, few studies have evaluated these aspects in the paediatric population[9,13,17-22].Here, we

evaluated in a paediatric population the association between MTX excretion and hepatic and kidney function changes, in order to better understand factors that may be predictive of the onset of OM. In general, our results demonstrated a high incidence of OM in paediatric patients, but we did not find evidence of an association between MTX clearance time and OM. Hepatic (ALT and AST) and renal markers (creatinine) were associated with OM in lymphoma patients.

In the present study, the inpatient children evaluated showed OM in 75% of 255 chemotherapy cycles with HD-MTX. Of these, 46.6% presented WHO grade of oral mucositis ≥ 2. These results are in accordance with current literature that has reported a prevalence range of 33 to 80% in paediatric chemotherapy patients[13,20,23]. In addition, OM has been reported to affect more than 50% of children receiving MTX therapy[23,24]. This value is variable because it depends of several factors, including the study methodology, infused doses and protocols adopted, concomitant administration of folic acid replacement, introduction of preventive measures for OM, hyperhydration, age group analysed and OM graduation system used for evaluation[20,25].

Our results, showing a high incidence of OM in paediatric patients, support the idea that it is crucial to adopt preventive protocols for OM in this group during treatment for leukaemia, osteosarcoma and lymphomas. It is important to reinforce that all patients were examined once a day after chemotherapy protocol started. When OM was clinically identified, a treatment protocol with daily photobiomodulation therapy was immediately initiated[16].This approach likely reduced the severity of OM during the following days and promoted oral mucosa healing[26]. We identified only 15.2% of our patients with WHO grades 3 and 4 (severe cases). In contrast, Otmani et al.[18] found 32.3% severe degrees of OM in patients who did not receive PBM treatment. Systematic reviews have shown positive results with the use of PBM for prevention and treatment of OM[22,27]. In our service, after the present study, a preventive protocol with PBM was instituted in the management of paediatric cancer patients undergoing HD-MTX.

Independently of the type of base disease, all groups presented high incidence of ulcerative grades of OM: 69.9% of leukaemia patients, 77.9% of osteosarcoma patients and 81.6% of lymphoma patients.

In lymphoma and leukaemia, the HD-MTX was used with other cytotoxic drugs. However, in osteosarcoma, it was administered only HD-MTX, and at doses of 12 g/m^2. OM can be associated with HD-MTX and other chemotherapy agents such as cisplatin, cytarabine and doxorubicin. Usually in the literature, leukaemia and lymphomas are evaluated together. It has been reported that children with haematologic malignancies showed an increase of 7.0 and 7.1 times in the risk of developing OM, compared with children with central nervous system and solid tumours, respectively[20]. Allen Importantly, paediatric cancers are rare, which is a challenge for clinical studies, particularly for analysis of specific subtypes of diseases. However, here we were able to evaluate leukaemia and lymphomas singly, and interesting findings were observed. Severe OM (grades 3 and 4) was different proportions with patients with lymphomas than with leukaemia and osteosarcoma (p= 0.01). Our results revealed that is important to try to evaluate separately the subtypes of haematologic diseases and the risk factors for toxicities including OM.

We also examined the relationship of HD-MTX excretion with OM status. No association was found between delayed excretion of MTX and OM development in the inpatient children analysed. This result agrees with Allen et al.[20] and Tsurusawa et al.[28] who also did not observe any association between OM and HD-MTX administration in pediatric population. During follow-up, in only 77 (30.2%) of 255 cycles, it was observed delayed MTX excretion, which may have influenced the lack of statistical association between delayed excretion and the development of OM. In contrast, other studies have reported that HD-MTX excretion delay is a risk factor for OM development[7,23,24]. In a pilot study published in 2007, Cheng et al.[23] found a statistically significant association between longer MTX excretion time (66 hours) and development of OM (OR = 8.2, 95% CI 1.4–47). Park and Shin[7] also demonstrated higher plasma MTX levels (48 hours and 72 hours) associated with OM (p = 0.007 and p = 0.046) in 37 paediatric osteosarcoma patients. It is important to highlight that in our institution, patients undergoing treatment with HD-MTX receive strict hyperhydration, regular folinic acid rescue, bicarbonate infusion and MTX serum level monitoring, which improves their general condition and could prevent the development of side effects. Additionally, when OM started, we implemented PBM therapy, which has been associated with improvement in OM

lesions. It is also important to discuss that genetic polymorphisms in the metabolic and cellular transport pathways of MTX could influence several clinical outcomes, such as response to therapy, duration of hospitalisation and development and severity of OM[11].

In leukaemia and osteosarcoma patients, no association was observed between OM and hepatic and renal enzyme analyses. However, when the three groups were analysed using Poisson regression, it was shown that the increase in BB levels increases the prevalence of OM, with a higher value associated with BI (39%). Further, patients with lymphoma who presented OM were positively associated with hepatic (higher ALT and AST) and renal alteration (higher creatinine values). Moreover, our research demonstrated by the prevalence ratio that alteration of levels by one unit is enough to increase the prevalence of OM by 37%. An association between increase of OM and some chemotherapy protocols has been reported[25,29]. Usually, patients with haematologic diseases present a higher incidence of OM compared to solid tumours[18,25]. In this study, the increase in total BB levels demonstrated an 11% higher prevalence of OM, and BI a 39% increase in the overall sample. BI is also usually associated with haematologic diseases, because it is formed with red blood cell destruction and may be altered with blood changes[29]. No studies were found that separately analysed BI and BD in paediatric patients, when analysing the relationship with OM.

HD-MTX has been associated with hepatic toxicity with elevated serum ALT and AST values, but these laboratory findings usually have no clinical significance and require no adjustment of subsequent courses of HD-MTX because most cases are transient and reversible[5].However, the association of HD-MTX with other chemotherapy agents can promote higher hepatic and renal dysfunction and can be associated with OM development. Thus, we suggest that the association between OM and hepatic and renal toxicity in our lymphoma patients was likely due to the use of HD-MTX with other chemotherapy agents (doxorubicin, cyclophosphamide and cytarabine). All of these agents used in lymphoma protocols have been associated with hepatic and renal toxicity, and it is not possible to determine only one drug as responsible for the toxicity issue[25].Our results are in agreement with other studies demonstrating the need for greater attention to lymphoma patients regarding toxicities, including OM[29,30]. In addition, other aspects such as immunologic

mechanisms of the host and genetic factors are very important and should be analysed in future studies to understand and prevent these toxicities[30].

Clinical research in this field is challenging since cancer in paediatric patients needing HD-MTX is not prevalent, and due to the necessity of many patients, and a wide variety of protocols that can cause toxicities. Furthermore, a limitation of our research is the inability to include patients who were receiving therapy on an outpatient basis. Despite these difficulties, in the present study, we were able to analyse a substantial number of cycles and the patients were closely followed from a clinical and laboratory perspective. Our results reinforce the need for identification of risk factors for OM to qualify and individualise preventive protocols.

CONCLUSIONS

OM was a prevalent complication in childhood cancer patients receiving HD-MTX, indicating that preventive measures against OM should be planned for these patients. Patients with lymphoma presented a greater risk of developing OM, with hepatic and renal toxicity indicating that close monitoring of these patients is necessary to predict, prevent and treat all toxicities. Additionally, no association was observed between HD-MTX clearance time and OM.

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Base Disease	Age			Gender		Time of infusion (h)	
	Mean (SD)	Min	Max	Male	Female	Mean (SD)	Median
				n (%)	n (%)		[p25;p75]
Leukaemia (n=48)	6.4 (4.2)	0	17	27 (56.3)	21 (43.8)	17.1 (9.0)	24 [6; 24]
Osteosarcoma (n=15)	12.2 (3.9)	6	17	7 (46.7)	8 (53.3)	4.0 (0.0)	4 [4; 4]
Lymphoma (n=14)	11.0 (4.5)	3	17	10 (71.4)	4 (28.6)	8.0 (8.7)	4 [3; 6]
Total (n=77)	8.36 (4,8)	0	17	44 (57.1)	33 (42.9)	10.2(9.0)	4 [3;24]

Table 1. Patient demographic characteristics and time of MTX-infusion, according to the base disease.

Table 2. Level of hepatic and renal biochemical markers in the oncological diseases analysed.

	Leukaemia	Osteosarcoma	Lymphoma	p-value
	(n=113)	(n=104)	(n=38)	
	Median [p25; p75]	Median [p25; p75]	Median [p25; p75]	
BB	0.3[a] [0.3; 0.5]	0.3[a][0.3; 0.5]	0,6[b][0.3; 1.2]	**0,002**
BD	0.2[b][0.1; 0.2]	0.2[ab][0.1; 0.3]	0,3[a][0.1; 0.7]	**<0,001**
BI	0.2[b][0.2;0.3]	0.2[a][0.2; 0.2]	0.2[b][0.2; 0.4]	**0,003**
AST	34.0[b][27.0; 44.0]	66.5[a][34.0; 146.0]	24.5[b][17.0; 45.0]	**<0,001**
ALT	40.0[b][22.0; 97.0]	118.0[a][51.5; 275.5]	31.0[b][21.0; 146.0]	**<0,001**
Urea	22.0[b][16.0; 29.0]	27.0[a][21.0; 33.5]	28.5[a][20.0; 40.0]	**<0,001**
Creatinine	0.35[b][0.29; 0.42]	0.56[a][0.40; 0.75]	0.47[a][0.37; 0.59]	**<0,001**

* Comparison performed by the Kruskal-Wallis Test; when significant, Dunn's post hoc test was used. Distinct letters represent categories with statistically distinct distributions.

Table 3. Occurrence of oral mucositis (grades according WHO classification), in the oncological diseases analysed.

		Leukaemia	Osteosarcoma	Lymphoma	p-value
		(n=113)	(n=104)	(n=38)	
		n (%)	n (%)	n (%)	
Oral mucositis (OM)	Abscence	34 (30.1)	23 (22.1)	7 (18.4)	0.236
	Present	79 (69.9)	81 (77.9)	31 (81.6)	
Ulcerative lesions	Absence (0 or 1)	69 (61.1)	50 (48.1)	17 (44.7)	0.082
	Present (2, 3 or 4)	44 (38.9)	54 (51.9)	21 (55.3)	
Severe mucositis	Abscence (0,1 or 2)	99 (87.6)	91 (87.5)	26 (68.4)	**0.01**
	Present (3 or 4)	14 (12.4)	13 (12.5)	12 (31.6)	

* Chi-square test. In bold analysis of adjusted standardized residuals greater than 1.96.

Table 4. Excretion time of MTX (expressed in hours) in the 144 cycles analysed, according the severity of OM and the oncological disease.

	Non-ulcerative OM			Ulcerative OM		
	Median [p25; p75]	min-máx	n	Median [p25; p75]	min-máx	n
Leukaemia (n=113)	72 [72; 72]	48 - 144	69	72 [48; 96]	24 - 240	44
Osteosarcoma (n= 104)	72 [72; 96]	48 - 144	50	72 [72; 96]	48 - 264	54
Lymphoma (n= 38)	72 [48; 72]	48 - 144	17	72 [60; 108]	48 - 192	21

Mann-Whitney's test

Table 5. Analysis of relationship of OM with renal and hepatic function in different diseases.

	OM	Leukaemia (n= 113)			Osteosarcoma (n=104)			Lymphoma (n=38)		
		n	Median [IC95%]	p-value	n	Median [IC95%]	p-value	n	Median [IC95%]	p-value
BB	Absence	34	0.401 [0.349; 0.461]	0.069	23	0.452 [0.340; 0.600]	0.918	7	0.537 [0.292; 0.988]	0.071
	Present	79	0.476 [0.414; 0.547]		81	0.459 [0.374; 0.565]		31	1.041 [0.699; 1.548]	
BBD	Absence	34	0.169 [0.138; 0.206]	0.102	23	0.247 [0.174; 0.349]	0.839	7	0.283 [0.140; 0.571]	0.075
	Present	79	0.208 [0.175; 0.247]		81	0.256 [0.190; 0.345]		31	0.617 [0.417; 0.912]	
BBI.	Absence	34	0.235 [0.207; 0.266]	0.077	23	0.222 [0.178; 0.278]	0.972	7	0.254 [0.138; 0.468]	0.152
	Present	79	0.274 [0.240; 0.312]		81	0.223 [0.196; 0.254]		31	0.399 [0.255; 0.625]	
AST	Absence	34	42.5 [28.9; 62.5]	0.811	23	104.4 [68.806; 158.281]	0.919	7	27.6 [19.4; 39.2]	**0.006**
	Present	79	44.8 [36.3; 55.3]		81	106.8 [81.083; 140.677]		31	43.1 [26.3; 70.6]	
ALT	Absence	34	51.4 [33.0; 80.2]	0.167	23	185.9 [111.0; 311.4]	0.83	7	42.1 [18.7; 94.8]	**0.04**
	Present	79	72.1 [55.4; 93.9]		81	197.6 [148.4; 263.1]		31	87.8 [53.9; 143.0]	
Urea	Absence	34	23.1 [19.5; 27.3]	0.852	23	25.7 [20.6; 32.2]	0.463	7	24.4 [18,4; 32,5]	0.021
	Present	79	22.6 [20.5; 25.0]		81	27.9 [25.1; 30.9]		31	33.5 [27.8; 40.3]	
Creatinine	Absence	34	0.427 [0,331; 0,550]	0.278	23	0.616 [0,503; 0,754]	0.815	7	0.394 [0.335; 0.463]	**0.008**
	Present	79	0.376 [0.338; 0.418]		81	0.601 [0.473; 0.763]		31	0.595 [0.451; 0.784]	

#GEE model -Gamma distribuction – dose-adjusted analyzes of each chemotherapy

BB=total bilirubin; BBD= direct bilirubin; BBI= indirect bilirubin; AST= aspartate aminotransferase; ALT= alanine aminotransferase

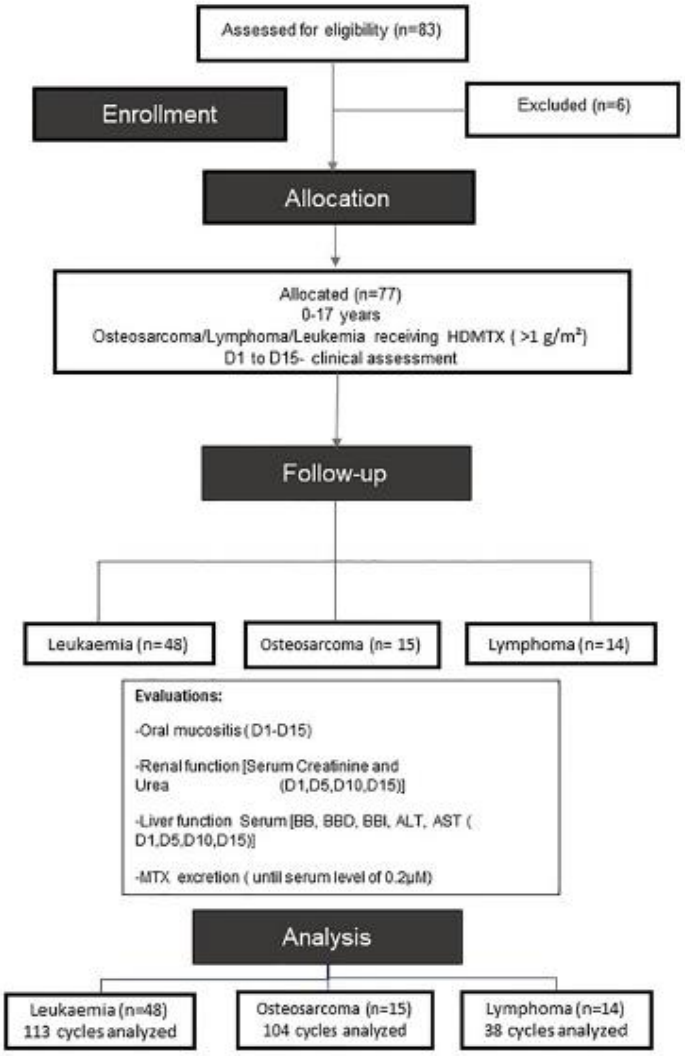
Figure Legends

Figure 1 Flowchart showing subject enrollment and follow-up.

BB=total bilirubin; BBD= direct bilirubin; BBI= indirect bilirubin; AST= aspartate aminotransferase; ALT= alanine aminotransferase

Why this paper is important to paediatric dentists

- Oral mucositis (OM) in childhood cancer is considered one of the most debilitating adverse effects of chemotherapy, and the knowledge of its risk factors is crucial for preventive and treatment measures.
- This study reinforces that OM is prevalent in childhood cancer patients receiving HD-MTX, indicating that preventive measures against OM should be planned for these patients.
- Additionally, patients with lymphoma presented a greater risk of developing OM, and hepatic and renal alterations described indicated that close monitoring of these patients is necessary to predict, prevent and treat adverse events.
- Preventive strategy for OM should be planned such as PBMT.



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4. ARTIGO CIENTÍFICO - 3

Incidence and risk factors for oral mucositis in pediatric patients receiving chemotherapy

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Este trabalho de conclusão de curso foi publicado na revista Support Care Cancer. 2021

Curra M, Gabriel AF, Ferreira MBC, Martins MAT, Brunetto AT, Gregianin LJ, Martins MD. Incidence and risk factors for oral mucositis in pediatric patients receiving chemotherapy.Support Care Cancer. 2021 Apr 12. doi: 10.1007/s00520-021-06199-5. Online ahead of print. PMID: 33846825 IF: 3.603/Qualis A2

Supportive Care in Cancer
https://doi.org/10.1007/s00520-021-06199-5

ORIGINAL ARTICLE

Incidence and risk factors for oral mucositis in pediatric patients receiving chemotherapy

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Received: 19 August 2020 / Accepted: 5 April 2021

Abstract

Purpose To investigate the incidence and risk factors for oral mucositis (OM) in patients with childhood cancer undergoing chemotherapy.

Methods Eight hundred and twenty-nine cycles of chemotherapy were evaluated in 112 patients with childhood cancer undergoing chemotherapy. Chemotherapy protocol, hematological, hepatic, and renal function parameters were collected and compared to presence and severity of OM, as graded by the World Health Organization (WHO) scale. Patients received counseling on oral hygiene and those who presented with OM (grade ≥1) received photobiomodulation therapy (PBMT).

Results Age ranged from 0 to 17 years (mean/SD, 8.58 ± 5.05) and fifty-one patients (45.54%) were females. The most common baseline diseases were leukemia (51%) followed by sarcomas (23%) and lymphomas (18%). Eight hundred and twenty-nine cycles of chemotherapy were evaluated, and OM was diagnosed in 527 cycles (63.57%). Higher incidence and severity of OM was observed in protocols using high-dose methotrexate (MTX-HD), MTX-HD cyclophosphamide/doxorubicin combination, and MTX-HD combined with cyclophosphamide ($p < 0.001$). Patients with severe OM had lower levels of leukocytes ($p = 0.003$), hemoglobin ($p = 0.005$), platelets ($p = 0.034$), and higher levels of total bilirubin ($p = 0.027$), alanine aminotransferase (ALT) ($p = 0.001$), and creatinine ($p = 0.007$).

Conclusion The study contributes to the elucidation of the risk factors for OM in pediatric cancer patients. Chemotherapy protocols using MTX-HD, MTX-HD associated with doxorubicin and cyclophosphamide, and MTX-HD and cyclophosphamide a have higher incidence of severe grades of OM. Other toxicities such as hematological, hepatic, and renal also developed in patients with OM.

Keywords Oral mucositis · Chemotherapy · Pediatric patients · Risk factors

Introduction

Childhood cancer represents 2–3% of all cancers and 6.7 million cases of childhood cancer are estimated worldwide between 2015 and 2030 with more than 450,000 cases per year [1]. The most common malignancies are leukemias and lymphomas, followed by central nervous system tumors, solid abdominal tumors (Wilms' tumor and neuroblastoma), and sarcomas. Treatment may include a combination of surgery, radiotherapy, and chemotherapy. Survival ranges from 70 to 97% for patients treated with well-established protocols in specialized cancer centers. Chemotherapy can be used in monotherapy but more commonly in combination regimes with agents that have synergism [2–4]. The chemotherapy protocols generally exhibit a narrow therapeutic window and, therefore, the differences between the doses that produce anti-tumor effects and those that lead to toxicity are small. The

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adverse effects during chemotherapy can influence the quality of life and the most common toxicities include vomiting, diarrhea, alopecia, fatigue, hematological, hepatic, renal toxicities, and oral mucositis (OM) [3–6].

OM is an inflammatory reaction in response to numerous chemotherapeutic agents and radiation therapy, particularly in the head and neck. The lesions develop due to chemotherapeutic agents that attack cells that divide rapidly. Clinically, OM presents as erythema and ulcerations with varying degrees of intensity. OM can affect the patient's nutritional status, be extremely painful and require the use of higher analgesic doses, increase the risk of infections, cause a reduction in the intensity of the chemotherapy dose, delay treatment, affect the quality of life, and prolong hospitalization [5–8]. In 2019, the Mucositis Study Group of the Multinational Cancer Support Association and the International Oral Oncology Society (MASCC/ISOO) guidelines described different protocols of photobiomodulation therapy (PBM) used to prevent or treat OM for patients submitted to chemotherapy [9]. Also, MASCC/ISOO published a clinical practice guideline for the management of oral mucositis in pediatric cancer patients [10]. In both protocols, it was suggested that the implementation of basic oral care protocol is very appropriate. Basic oral care involves multi-agent combination oral care protocols (daily oral hygiene with a soft toothbrush and toothpaste, and mouthwash with normal saline, sodium bicarbonate mouthwash), patient education, and chlorhexidine. Visits to a dentist before, during, and after oncologic treatment are recommended to ensure the identification and treatment of oral complication. Oral cryotherapy (placing ice chips or popsicles in the mouth) is recommended to prevent oral mucositis in patients receiving bolus 5-Fluorouracil. For the OM treatment, the use of opioids, topical anesthetics; anti-inflammatory agents, antibacterial, antifungal, and antiviral agents; mucosal barriers and coating agents; cytoprotectants; and the use of PBM have been suggested [6–11].

Factors associated with OM have been described in the literature, including type of chemotherapy drugs, chemotherapy doses, age, nutritional status, and gene polymorphisms that encode enzymes responsible for the metabolism, transport, and excretion of chemotherapy drugs. Also, other important toxicities such as hematological, renal, and hepatic could be observed in concomitance with OM [12–16]. Children with hematologic malignancies experience mucositis more frequently than those with solid tumors, as do those with bone marrow transplantation with myeloablative protocols. The prevalence of mucositis in the pediatric population receiving chemotherapy is greater than in adults, as this may be due to rapid cell division and dose intense regimes as well. However, there are few studies describing the severity of OM and the association with different treatment protocols used in the pediatric population. Here, the incidence and severity of OM in pediatric oncological patients and its relationship with the chemotherapy protocols as well as hematological, hepatic, and renal toxicity are shown.

Materials and methods

This prospective cohort study was conducted at Pediatric Oncology Service at Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil, following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guideline for Reporting *cohort studies*. In addition, this study received approval from the Institutional Human Research Ethics Committee (HCPA protocol 14-0581 and CAEE 40921215.6.0000.5327). Patients and/or their legal guardians signed an informed consent.

Study population

One hundred and eighteen inpatients and outpatients admitted to the Pediatric Oncology Service from January 2015 to October 2018 were evaluated by convenience. One hundred twelve patients aged 0 to 17 years with a diagnosis of childhood cancer were included in this study; these patients were receiving any protocol chemotherapy. Only patients who received first-line chemotherapy were included. Patients who received radiotherapy to the head and neck and patients with relapsing or refractory disease were excluded (n=6).

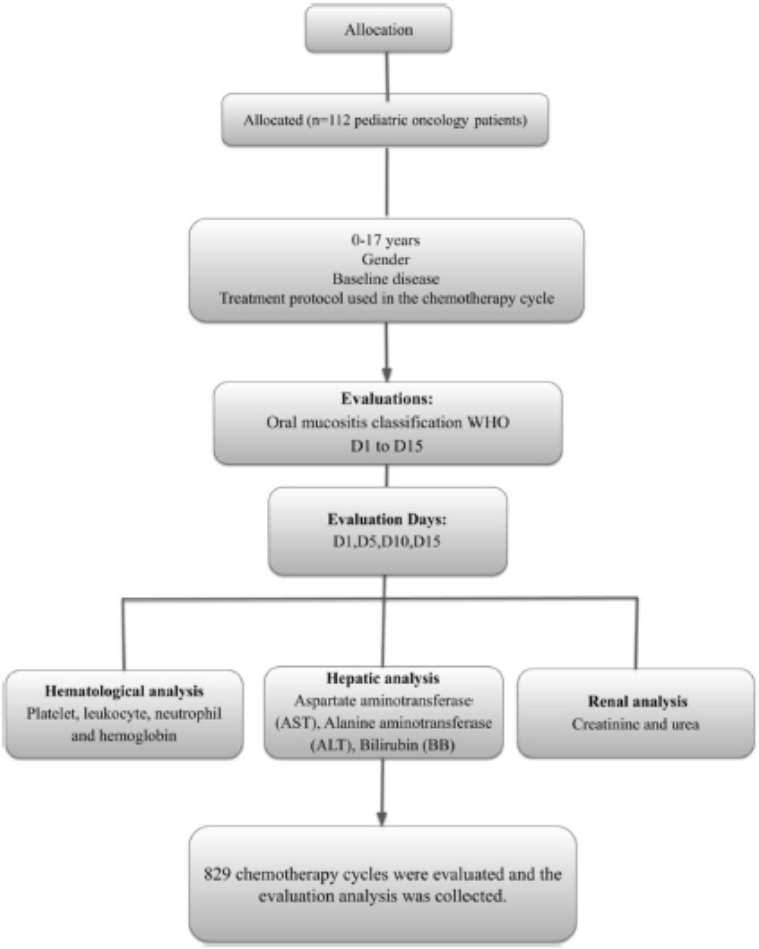
All patients and families received oral hygiene instructions at the beginning of treatment that included counseling on tooth brushing with soft brushes and rinsing with chlorhexidine digluconate (0.12%). The patients were referred to the odontology department when indicated before the commencement of chemotherapy.

Procedures

Figure 1 displays the study flowchart. Demographic data and treatment characteristics were collected at baseline and follow-up visits. The chemotherapy protocol was defined by the treating physician and patients were managed according to institutional guidelines. Patients were followed during each chemotherapy cycle from day 0 until day 15 independently of the duration of chemotherapy protocol.

For better data organization and statistical analysis, the protocols used in each course were grouped into 8 different types, based on the groups of drugs used. The name of the protocol was given based on the most stomatotoxic drug. All patients receiving MTX chemotherapy also received hyperhydration, bicarbonate to decrease renal MTX globule precipitation, and leucovorin rescue, with dose adjustments (according to the MTX concentration curve, estimated every 24 h) to reduce the development of adverse effects. Blood samples were routinely performed for analysis of

Fig. 1 The study flowchart



hematological parameters (platelet, leukocyte, neutrophil, and hemoglobin), hepatic functions (aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (BB)), and renal (creatinine and urea). For laboratory data analysis, the highest or lowest value within each cycle was considered and classified in grades according to the National Cancer Institute (NCI) classification (Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0CTCAE v5.0 – November 27, 2017) [17]. Urea values up to the normal limit (48 mg/dL) were considered grade 0 and above 48mg/dL, grade 1.

Oral mucositis was evaluated daily, from D1 until D15 by two calibrated dentists. The World Health Organization (WHO) scale was used: grade 0 = no mucositis; grade 1 = erythema without lesions; grade 2 = ulcers, but able to eat; grade 3 = painful ulcers, but able to consume liquid food (nutrition) with analgesia for support; grade 4 = requires parenteral or enteral support and continuous analgesia. Patients who presented OM (grade≥1) received PBM treatment following the protocol previously described by Weissheimer [18]. For the purposes of statistical analysis, the worst grade of OM in each evaluated cycle was considered.

Statistical analysis

The proportions of the protocol variable were associated between the degree of oral mucositis by the chi-square test. To verify the direct local association, an analysis of standardized

residues with values greater than 1.96 was used. For the quantitative variables, the Shapiro-Wilk normality test was performed to verify the distribution of each variable between the degrees of oral mucositis. Classifying as asymmetric variables, we compared the distributions of the variables between the degrees of oral mucositis using the Kruskal-Wallis test. When significant, it was compared by Dunn's post hoc test. Analysis of the ROC curve was performed to verify the best cutoff point for the worst leukocyte variables, platelets, hemoglobin, bilirubin, and creatinine among the categorization of the mucositis variable. There were 3 models performed: the first dichotomizing the changeable mucositis in degrees 0 vs 1 to 3; the second dichotomizing in degrees 0 or 1 vs 2 or 3; the third one dichotomizing in 0 to 2 vs 3. The areas with their respective standard errors, the significance of this area (compared to the reference value 0.5), and, when significant, the cutoff value were indicated, followed by the sensitivity and specificity values. Youden's index was used to select the most suitable. Logistic regression was performed, estimating the odds ratio (odds ratio = OR) and its 95% confidence interval to show the relationships between the categories of variables studied in relation to the outcomes. Initially, the not-adjusted chance ratio (univariate model) was calculated. Then, for variables with a p value less than 0.10, the multivariable model was performed. A binary logistic distribution with a likelihood ratio chi-square statistic was used. The outcomes for OM were evaluated in two different classifications: (1) according to absence and presence of ulceration (non-ulcerated OM (grades 0 and 1) and ulcerative OM (grades 2, 3, and 4) or (2) according to OM severity (mild/moderate OM (grades 0, 1, 2) and severe OM (grades 3 and 4). The level of significance adopted was 0.05. The analyses were performed in SPSS v.25.

Results

Patient characteristics

As shown in Table 1, one hundred and twelve patients were included over 4 years of follow-up (2015–2018). The patients were submitted to 829 chemotherapy cycles throughout their treatment. The average follow-up time for patients was 6 to 18 months.

OM is associated with chemotherapy protocol

Based on the fact that the treatment of pediatric cancer patients may involve different chemotherapy protocols throughout the chemotherapy cycles, we decided to present the results according to the protocol used for the individual patient. Table 2 shows the distribution of the protocols used, with the most used being doxorubicin (n = 227; 27.3%), MTX-HD (n = 200; 24.1%), followed by cytarabine, etoposide, carboplatin, and others (n = 111; 13.4%).

Of the 829 cycles of chemotherapy, OM were diagnosed in 527 cycles (63.57%). OM grade 1 was observed in 238 (28.71%) cycles; grade 2 in 219 (26.42%) cycles; and grades 3 and 4 in 70 (8.44%) cycles. There was an association between OM grade and chemotherapy protocol (p <0.001) as detailed in Table 3. The absence of OM was associated with protocols using cyclophosphamide, cytarabine, etoposide, and carboplatin (p <0.001). Patients who received low doses of MTX were associated with grade 1 OM (p <0.001). Grade 2 of OM was associated with the protocol that used MTX-HD alone (p <0.001). Severe OM (grades 3 and 4) was directly associated in greater proportion to the protocols that used MTX-HD + cyclophosphamide + doxorubicin and MTX-HD + cyclophosphamide. Analyzing the OM as non-ulcerative (grades 0 and 1) and ulcerative manifestation (grades 2, 3, and 4), an association between ulcerated lesions and MTX-HD and MTX- HD + cyclophosphamide + doxorubicin was observed (p <0.001) in Table 3.

Hematological toxicity is associated with OM severity

Patients with severe OM (grades 3 and 4) also presented lower leukocyte levels (p = 0.003), hemoglobin (p = 0.005), and platelets (p=0.034). Each increase of one unit of total leukocyte reduced the severity of OM (grades 3 and 4) by 23% (p= 0.028).

Hepatic and renal toxicity are associated with severe OM

Higher total bilirubin levels were associated with severe OM (grades 3 and 4) (p = 0.027). When assessing the odds ratio, the increase of one unit of total bilirubin increased severe OM (grades 3 and 4) by 45% (p=0.022). Another marker of liver toxicity, ALT showed higher levels in patients with OM grades 2, 3, and 4 (p = 0.001). Moreover, the increase of ten units of ALT increased ulcerative OM (grades 2, 3, and 4) by 3.48% (p=0.015). Increased creatinine was associated with severe OM grades (3 and 4) (p=0.07).

ROC curve demonstrated the development of severe grade of OM was associated with toxicity markers

ROC curve analysis was performed to verify the sensitivity and specificity of leukocyte, hemoglobin, platelets, total bilirubin, and creatinine values in the development of OM. Patients with less than $< 500 \times 10^3/mm^3$ leukocytes presented a higher risk of developing severe OM (specificity 0.8). Patients with hemoglobin less than 8.6 showed an increased risk of severe OM (sensitivity 0.79). Patients with less than 126,000 platelets also had a higher risk for severe OM (sensitivity of 0.77).

Table 1 Patient distribution according to demographic characteristics and type of cancer

Variable	Absolute frequency (*n*)	Relative frequency (%)
Number of patients	112	100
Gender		
Male	61	54.4
Female	51	45.5
Age, years (mean ± SD)	8.58 (± 5,05)	
Diagnosis	112	100
Acute lymphoblastic leukemia	50	44.64
Acute myeloid leukemia	8	7.14
Lymphomas	21	18.75
Sarcomas	26	23.21

Discussion

OM is a common and important toxicity associated with chemotherapy use in childhood cancer. OM can cause interruption of treatment, dose reductions, prolonged hospitalization, increased opioid use, and the risk of secondary infections [6, 11, 12, 19, 20]. The incidence and severity of OM in adult cancer are well known and depend on the type of protocol used in regard to specific agents and dose schedules [14, 21]; however, fewer studies in pediatric oncology have been conducted. Here, we evaluated the incidence and risk factors for OM in patients with childhood cancer undergoing chemotherapy. Our main results demonstrated that some chemotherapy protocols were associated with a higher incidence of severe grades of OM. In addition, we demonstrated that other toxicities such as hematological, hepatic, and renal occurred in association with the severity of OM.

In the present study, 112 pediatric oncological patients were evaluated in a total of 829 cycles of chemotherapy. We describe the incidence and severity of OM associated with the type of protocol and the impact of hematological, hepatic, and renal toxicity. The overall incidence of OM in our subset of pediatric patients was 63.57% and 8.44% presented with severe OM grades (grades 3 and 4). In similar studies, the overall incidence of OM varies from 18 to 80% and from 14 to 18.6% for severe grades [12, 19–24]. These variations in OM incidence may occur due to differences in each study regarding methodology, tumor types, chemotherapy combinations, type of prophylaxis used, and genetic background. Many of them did not offer any treatment for OM, or OM was not evaluated during all weeks of the chemotherapy cycles. It is important to emphasize that patients who had clinical signs of onset of OM, in the present study, received treatment with PBM as soon as they were identified. PBM was used as a treatment to reduce the severe manifestation of this injury and probably, for this reason, our percentages of severe OM were very low. It is well known that PBM decreases the severity of OM by accelerating tissue repair, reducing its severity, and decreasing pain [9, 12, 16, 18, 25–27]. Despite several studies that reported the benefit of preventive PBM protocol

Table 2 Distribution of chemotherapy protocol and number of cycles

Protocol	Type of chemotherapy agent	Cycles
1	Methotrexate high dose (MTX-HD) (>1 g/m^2)*	200 (24.1%)
2	Doxorubicin**	227 (27.3%)
3	MTX- HD + cyclophosphamide (1 g/m^2/cycle) + doxorubicin (25 mg/m^2/cycle)	60 (7.3%)
4	Methotrexate low dose (< 1 g/m^2)	57 (6.9%)
5	MTX- HD + cyclophosphamide	21 (2.5%)
6	Cyclophosphamide***	93 (11.3%)
7	Cytarabine (500 mg–9 g/m^2/cycle), etoposide (500 mg/m^2/cycle), carboplatin (400–500 mg/m^2/cycle).	111 (13.4%)
8	Cyclophosphamide (1.2 g/m^2/cycle) + doxorubicin (70 mg/m^2/cycle)	60 (7.2%)
	Total	829 (100%)

*MTX in osteosarcomas, the dose used was 12 g/m^2/cycle. In leukemia, the dose used varied from 5 to 8 g/m^2/cycle

**Doxorubicin alone or with other drugs than cyclophosphamide and MTX. In osteosarcomas, the dose used was 75 mg/m^2/cycle, in neuroblastoma and leukemia (30 mg/m^2/cycle)

***Cyclophosphamide alone or with other drugs than doxorubicin and MTX. In leukemias and neuroblastoma, the dose used was 1 g/m^2/cycle) and in medulloblastomas, it was cyclophosphamide 2 g/m^2/cycle

Table 3 Incidence and of risk factors for oral mucositis in pediatric patients receiving chemotherapy

Protocol	Total	OM grades				*p*
	n (%)	Grade 0 *n* (%)	Grade 1 *n* (%)	Grade 2 *n* (%)	Grades 3 and 4 *n* (%)	
MTX-HD	200 (100)	56 (28)	54 (27)	69 (34.5)	21 (10.5)	<0.001
Doxorubicin	227 (100)	80 (35.2)	70 (30.8)	64 (28.2)	13 (5.8)	
MTX-HD + cyclophosphamide + doxorubicin	60 (100)	14 (23.4)	9 (15)	20 (33.3)	17 (28.3)	
MTX low dose	57 (100)	14 (24.6)	23 (40.3)	17 (29.9)	3 (5.2)	
MTX- HD + cyclophosphamide	21 (100)	5 (23.7)	6 (28.5)	4 (19.3)	6 (28.5)	
Cyclophosphamide	93 (100)	43 (46.2)	25 (26.8)	21 (22.6)	4 (4.4)	
Cytarabine, etoposide, carboplatin	111 (100)	69 (62.1)	28 (25.3)	12 (10.8)	2 (1.8)	
Cyclophosphamide + doxorubicin	60 (100)	21 (35)	23 (38.4)	12 (20)	4 (6.6)	

for OM, the last guideline published by the Mucositis Study Group of the Multinational Cancer Support Association and the International Oral Oncology Society (MASCC/ISOO) recommended only for patients with hematopoietic stem cell transplantation, head and neck (H&N) radiotherapy (without chemotherapy), and H&N radiotherapy with chemotherapy. The use of PBMT in the prevention of oral mucositis, in patients undergoing chemotherapy, is still not yet recommended due to the lack of evidence and based on fact that we do not have studies that define which chemotherapeutic protocol patients will develop OM, especially the severe grades.

Different chemotherapeutic agents are used in the treatment of childhood cancer and some protocols are highly toxic due to their lack of specificity, causing damage to non-tumor cells [27, 28]. However, in the child group, there are few studies that directly link OM and different chemotherapeutic agents and combination in the same protocol. Our study demonstrated an association between OM and chemotherapy agents with increased risk for MTX-HD monotherapy or combination with cyclophosphamide and or doxorubicin (p <0.001). In our study, MTX-HD chemotherapy was directly associated with grade 2 OM. Combined MTX-HD + cyclophosphamide + doxorubicin and MTX-HD + cyclophosphamide chemotherapy was associated with severe OM (grades 3 and 4). When the analysis was performed by division into ulcerated and non-ulcerated lesions, the chemotherapeutic drugs MTX-HD and MTX-HD + cyclophosphamide + doxorubicin were associated with ulceration grades 2, 3, and 4 of OM. These results are very important to predict which patient has a higher chance to develop OM and select for those who need prophylactic protocols with PBMT in future studies.

Methotrexate (MTX) is an important chemotherapy used to treat acute lymphoblastic leukemia (ALL), osteosarcomas, and lymphomas [29–32]. The results of our study demonstrated that MTX-HD was associated with the development of the ulcerative form of OM and, when associated with other drugs, such as cyclophosphamide and doxorubicin, the severity of OM increases. Studies have shown that MTX-HD chemotherapy has been well described for its association with OM. Oosterom [32] reported that 23% of the children participating in the study who used MTX-HD for the treatment of ALL had severe OM. Another study by de Hoed [31] showed that 20% of pediatric patients had OM and this was associated with the use of MTX-HD. These studies corroborate our findings, in which MTX-HD was associated with 45% of ulcerated and severe OM in patients with pediatric cancer.

Doxorubicin and cyclophosphamide are important chemotherapeutic agents used to treat sarcomas, Hodgkin's lymphomas, and other neoplasms. In some cases, they are also associated with MTX especially for the treatment of osteosarcoma, non-Hodgkin's lymphoma, and acute lymphoblastic leukemia (ALL) [29, 33–36]. There are few studies associating these chemotherapeutic agents with the incidence of OM, and there are no studies that directly associate them with the development of OM in pediatric cancer patients. In our study, the protocols that combined the chemotherapeutic drugs MTX-HD, doxorubicin, and cyclophosphamide and MTX-HD and cyclophosphamide had severe grades of OM (grades 3 and 4). MCTieman [36] showed that in a specific protocol used in patients with osteosarcoma composed of doxorubicin and cisplatin, severe mucositis was observed in 43% of patients.

It is well known that several chemotherapeutics agents used for oncological treatment can cause other toxicities (hematological, hepatic, and renal) than OM [37–45]. All these side effects are mainly related to the type of drug and the therapeutic regimen used. However, it has been investigated whether the presence of other toxicities can be associated with the worsening of the OM. In this sense, regarding myelosuppression, our study demonstrated that lower levels of leukocytes (p = 0.003), hemoglobin (p = 0.005), and platelets were associated with OM in severe degrees (degrees 3 and 4). Our results also demonstrated by means of the ROC curve that verifies the sensitivity and specificity that patients with leukocytes <0.5 × 103 /mm^3 are at a higher risk of developing

OM grade 3. Patients with platelets less than ≥75– <200 × 103/mm^3 also had an increased risk of developing grade 3 OM. In addition, a 23% increase in leukocyte levels can reduce the chances of severe OM. Similar to our results, Damascena et al. [24] evaluated 142 pediatric cancer patients over 4 years and found that a low white blood cell count and the occurrence of OM were correlated. The association of OM with myelosuppression can be justified by the fact that the decrease in the count of neutrophils, leukocytes, and platelets interferes with an important inflammatory and healing response during the damage caused to the oral mucosa by chemotherapy [12, 40]. Based on our results, we suggest that it is very important to check the counts of these blood tests to determine the risk that these patients will develop more severe forms of OM.

As mentioned, hepatotoxicity is an important event associated with some chemotherapy agents [40]. In the present study, MTX was frequently used and is considered one important risk factor for hepatotoxicity and OM. Interestingly, an association of the two variables (OM and hepatoxicity) was demonstrated. Severe OM (grades 3 and 4) was associated with elevated hepatic levels of total bilirubin ($p = 0.027$). Also, OM grades 2, 3, and 4 (ulcerative forms of OM) were associated with increased levels of ALT ($p = 0.001$). Our results indicated the association of the impairment in hepatic function with the severity of OM. Also, renal function evaluation (creatinine clearance) is important during the chemotherapy treatment, as many drugs can be nephrotoxic (MTX, doxorubicin, cyclophosphamide) [43]. Our study found an association between increased creatinine levels and severe OM ($p = 0.007$). Some studies reported that high-dose of MTX (HD-MTX) excretion delay may be associated with a higher concentration of MTX in the bloodstream, consequently increasing the risk for OM [31, 44, 45]. In a previous study of our group [45], an association between OM and hepatic and renal toxicity in lymphoma patients receiving HD-MTX with other chemotherapy agents (doxorubicin, cyclophosphamide, and cytarabine) was described. So, it is important to monitor the hepatic and renal function in pediatric oncologic patients to better understand the association of OM with other toxicities and the general patient's condition during the treatment.

Our findings are important because they demonstrate which specific chemotherapeutic drugs and combinations are related to the severity of OM in the pediatric population. Also, we demonstrated that hematological, hepatic, and renal toxicities were associated with the worsening of OM. The greatest difficulty in discussing our findings is that the literature so far groups patients by type of disease (leukemia, lymphoma, osteosarcoma) or chemotherapy class (antimetabolites, alkylating, and natural) and not by chemotherapy protocol. In our opinion, a more personalized assessment of OM based on the most detailed identification of the protocol (combination and dose of drugs) is necessary. Our results demonstrate the need to invest in preventive OM care, especially in pediatric patients that have more risk to develop severe grades of OM such as submitted to protocols with MTX-HD isolated or combined to cyclophosphamide and doxorubicin. In addition, new studies to evaluate the effectiveness of preventive use of PBM in this group of patients are necessary.

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Conclusions

OM in pediatric cancer patients represents an important toxicity and is related to the type of chemotherapy protocol. Patients that received MTX-HD; combination chemotherapy of MTX-HD, doxorubicin, and cyclophosphamide; and MTX-HD and cyclophosphamide have a higher incidence of severe grades of OM. Other toxicities such as hematological, hepatic, and renal also are associated with with worsening OM in pediatric cancer patients

Acknowledgments The authors are grateful to all the members of the Pediatric Oncology Service of Porto Alegre Clinical Hospital (HCPA/UFRGS) for support during the development of the present research.

Availability of data and material Authors have full control of all primary data and allow the journal to review the data.

Code availability Not applicable

Author contribution Marina Curra: conceptualization; data curation; formal analysis; investigation; writing—original draft; writing—review and editing. Amanda F. Gabriel: conceptualization; data curation; formal analysis; investigation; writing—original draft; writing—review and editing. Maria Beatriz C. Ferreira: conceptualization; writing—review and editing. Marco Antonio T. Martins: conceptualization; data curation; writing—original draft; writing—review and editing. André T. Brunetto: conceptualization; data curation; formal analysis; writing—review and editing. Lauro J. Gregianin: conceptualization; data curation; formal analysis; writing—review and editing. Manoela D. Martins: conceptualization; data curation; formal analysis; investigation; methodology; project administration; writing original draft; writing—review and editing.

Funding This study was supported by the PRONON/Ministry of Health, Brazil (grant no. 25000.056.976/2015-52); Postgraduate Research Group of Porto Alegre Clinics Hospital (GPPG/FIPE: 2016-0608), Brazilian National Council for Scientific and Technological Development (CNPq student scholarship), Children's Cancer Institute (student scholarship), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brasil (CAPES)- finance code 001. Rafael Roesler and Manoela Domingues Martins are research fellows funded by the Brazilian National Council for Scientific and Technological Development (CNPq).

Declarations

Ethics approval Institutional Human Research Ethics Committee (HCPA protocol 14-0581 and CAEE 40921215.6.0000.5327).

Consent to participate Patients and/or their legal guardians signed an informed consent.

Consent for publication Patients and/or their legal guardians signed an informed consent with consent for publication.

Conflict of interest The authors declare no competing interests.

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5. CONSIDERAÇÕES FINAIS

Os estudos apresentados fornecem evidências científicas que o desenvolvimento e severidade da MO está relacionada a diferentes fatores, que podem ser descritos como fatores de risco. Agentes quimioterápicos incluídos no tratamento antineoplásico infantil como o MTX e suas combinações com doxorrubicina e/ou ciclofosfamida foram identificados tanto na revisão sistemática como nos estudos observacionais realizados no presente trabalho como importantes fatores de risco para o desenvolvimento de MO especialmente na sua forma severa. O tipo de agente quimioterápico está diretamente relacionado com o desenvolvimento e principalmente com a gravidade da MO. Desta forma, pacientes recebendo tratamento com estes fármacos devem ser acompanhados e tratados preventivamente. Outros importantes achados são que a toxicidade renal, hepática e hematológica devem ser monitoradas durante o curso do tratamento antineoplásico pois estas toxicidades ocorrem concomitantes ao desenvolvimento de quadros graves de MO, sendo que o tratamento de ambas as toxicidades associadas, são importantes para uma melhora no quadro geral do paciente.

A identificação de todos estes fatores torna-se importante para a realização de um tratamento individualizado, preventivo e eficaz para os pacientes que apresentam um risco maior de desenvolver formas graves destas lesões, pois a severidade da MO está diretamente relacionada a sua morbidade. Sendo assim, pacientes que apresentam maior risco de desenvolverem lesões graves de MO, podem ser prioritários em medidas preventivas de MO o que seria impactante na qualidade de vida do paciente com câncer infantil.

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