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ORIGINAL ARTICLE

Evaluation of GVHD And oral mucositis in patients submitted to HSCT at the STMO-CHC of UFPR

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Abstract:

Oral graft-versus-host disease (GVHD) and oral mucositis (OM) are important complications of hematopoietic stem cell transplantation (HSCT) that significantly impact the patient's quality of life. In this context, this study aimed to evaluate the profile of patients undergoing allogeneic HSCT, assessing oral GVHD and OM occurrence. Data from medical records of patients that underwent HSCT between 2019 and 2021 were collected. Patients over 18 years old, with diseases or conditions requiring HSCT, were included. A clinical examination was performed to evaluate the occurrence of GVHD and OM. A total of 47 patients undergoing HSCT were evaluated of which 34.04% developed GVHD, and of these 81.25% have had oral involvement. As for OM, it affected 82.97% of the patients, with grades 3 and 4 being more detected. The most frequent previous disease was acute myeloid leukemia, and most of these patients received a related type of transplant (84.61%), fully compatible (53.84%), with bone marrow as a source of stem cells (53.84%). Most patients received the myeloablative conditioning regimen (69.23%). Cyclosporine was the most immunosuppressive agent used for the GVHD prevention associated with methotrexate (76.92%). Oral GVHD and OM are frequent and debilitating oral complications of HSCT, which can compromise a patient's general health and overall survival. Early diagnosis is important for a quick start of treatment and to reduce the impact on the patient's prognosis.

Keywords: Hematopoietic Stem Cell Transplantation; Transplantation Conditioning, Graft versus Host Disease; Mucositis; Mouth.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is an important method of treatment for patients with inherited or acquired malignant and non-malignant disorders, including hematologic, immunologic, or autoimmune disorders[1-7]. Matching between donor and recipient is based on the variability of the HLA gene (human leukocyte antigens) and a perfect match is ideal[1,3,6].

Before transplantation, patients receive a conditioning regimen (CR) through chemotherapy (QT) alone or combined with radiotherapy (RT), which makes it possible to reduce or destroy the underlying disease and the recipient's immune system, allowing the engraftment of hematologic stem cells (HSC) and transplant acceptance[1,3,6,8]. CRs include myeloablative (MA), reduced intensity (RIC), and non-myeloablative (NMA)[3,8-11]. Despite being fundamental, these CR, especially MA, are associated with toxicity, risk of transplant-related mortality, and the appearance of other complications, such as oral graft-versus-host disease (GVHD) and oral mucositis (OM)[2,8-10,12,13].

GVHD is one of the main complications of HSCT and an important cause of morbidity and mortality, with a profound impact on quality of life[2,4-7, 11,14-17]. Most allogeneic transplant recipients develop some degree of the disease[3] despite prophylaxis with immunosuppressants[18]. It can affect one or more organs, mainly the skin, liver, and gastrointestinal tract, including the oral cavity[1-7,14,16,17]. The condition can manifest itself in an acute (GVHD) or chronic form (cGVHD)[2,3,6,14], according to the clinical manifestations and pathological characteristics[5,6,17]. The oral cavity is frequently affected by cGVHD[2,14,17] and manifests as whitish lesions, similar to oral reticular lichen planus, and may also present ulcerations, mucoceles, xerostomia, limited mouth opening, and mucosal atrophy[2,4,5,14] (Figure 1), with an impact on oral general health[2,4,5,6,16].

Figure 1. Intraoral photographs of a patient who presented oral GVHD, in (A) buccal mucosa, (B) tongue, and (C) lower lip, manifested as whitish lines with the presence of ulcers, and (C) mucocele in the lower lip.

OM is an early, debilitating, and common adverse effect of HSCT[10,13,19,20], affecting approximately 80% of the patients[13,21,22]. It ranges from erythematous atrophic lesions of the mucosa to extensive ulcerations (Figure 2), associated with discomfort, burning sensation, secondary infections, pain, and impairment of oral and systemic functions[2,19-25].

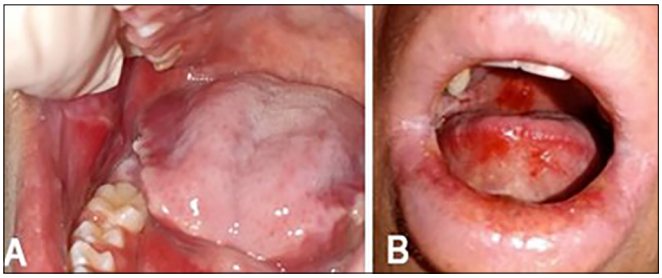

Figure 2. Intraoral photograph indicating the presence of oral mucositis, specifically on the edge and apex of the tongue (A and B), buccal mucosa (A), floor of the mouth (A), and lower lip (B), characterized by reddened areas which may be associated with ulcers, pain, and impaired function.

Considering the impact of oral complications on morbidity, mortality, and survival of individuals undergoing HSCT, this study aimed to analyze the sociodemographic, clinical, and therapeutic profile of patients undergoing HSCT, and correlate to the manifestations of oral complications with emphasis on the assessment of oral GVHD and OM.

MATERIALS AND METHODS

This study was approved by the Institutional Research Ethics Committee under protocol 4.414.355, and patients who agreed to participate in the research signed a Free and Informed Consent Term. It was a longitudinal observational study that evaluated patients over 18 years between 2019 and 2021 who underwent HSCT. Medical data were collected from hospital records and included information from clinical examinations. The information collected included the patient's sociodemographic data (sex and age), and HSTC information (underlying disease, type of transplant, compatibility, HSC source, conditioning regimen, and immunoprophylaxis for GVHD). The occurrence of GVHD and OM was assessed after clinical examination. Oral GVHD and OM were classified according to the NIH 2014[26] and MASCC/ISOO 2020[20] guidelines, respectively, using the WHO scale for OM classification[23,25], and the presence or absence of oral GVHD and OM. A follow-up was performed

periodically pre-HSCT and on days 15, 30, 60, 90, and 120 post-HSCT.

Afterward, the information collected was tabulated in a spreadsheet in Excel for Windows software and the results were analyzed.

RESULTS

The main results found in this study can be observed in Table 1.

The sample consisted of 47 patients, most of them male, aged between 19 and 62 years old. The patients most often presented severe aplastic anemia as a hematological disease before HSCT, followed by acute myeloid leukemia and acute lymphocytic leukemia.

In most cases, the donor was related, and fully compatible, having bone marrow as the source of HSC. As for the conditioning regimen, in most cases, MA was used, and for immunoprophylaxis for GVHD,

Table 1. Sociodemographic, clinical and therapeutic profile of patients who underwent allogeneic HSCT.

	General sample		Oral GVHD		OM	
Samples	**n**	**%**	**n**	**%**	**n**	**%**
No. of patient	47	100	13	27.65	39	82.97
Sex						
Male	28	59.57	10	76.92	24	61.53
Female	19	40.42	3	23.07	15	38.46
Average age (years)	37.31		40.15		38,74	
Underlying disease						
AAS	15	31.91	2	15.38	11	28.20
AML	14	29.78	4	30.76	13	33.33
ALL	8	17.02	2	15.38	8	20.51
NHL	4	8.51	3	23.07	2	5.12
MS	3	6.38	2	15.38	3	7.69
O	2	4.25	0	0	2	5.12
HL	1	2.12	0	0	0	0
Type of transplant						
related	31	65.95	11	84.61	25	64.10
unrelated	16	34.04	2	15.38	14	35.89
compatibility						
compatible	26	55.31	7	53.84	22	56.41
not compatible	21	44.68	6	46.15	17	43.58
HSC source						
Bone marrow	35	74.46	7	53.84	30	76.92
Peripheral blood	12	25,53	6	46,15	9	23,07
Conditioning regimen						
MA	38	80,85	9	69,23	34	87,17
RIC	8	17,02	3	23,07	4	10,25
NMA	1	2,12	1	7,69	1	2,56
Immunoprophylaxis for GVHD						
CSA + MTX	40	85,10	10	76,92	35	89,74
CSA + MMF + G-CSF	1	2,12	1	7,69	1	2,56
Cy 100 + CSA + MMF	6	12,76	2	15,38	3	7,69

LEGEND - OM: oral mucositis; n: number of cases; AAS: severe aplastic anemia; AML: acute myeloid leukemia; ALL: acute lymphocytic leukemia; NHL: non-Hodgkin's lymphoma; MS: myelodysplastic syndrome; O: others; HL: Hodgkin's lymphoma; MA: myeloablative; RIC: reduced intensity regimen; NMA: non-myeloablative; CSA: cyclosporine; MTX: methotrexate; MMF: mycophenolate mofetil; G-CSF - growth factors; Cy: cyclophosphamide.

the most used drug protocol was cyclosporine associated with methotrexate (CSA + MTX).

In this study, 16 patients developed GVHD (34.04%), and of those, 13 had oral GVHD (81.25%). Considering the total number of the sample, 27.6% of patients presented oral GVHD. Most patients were male, between 21 and 62 years old (mean age of 40,15 years), with acute myeloid leukemia as the most frequent previous disease, and submitted in most cases to a related, fully compatible bone marrow transplant. The most frequent conditioning regimen used was myeloablative, and for immunoprophylaxis for GVHD, CSA + MTX.

Oral Mucositis was assessed and affected most patients (82.97%), with grades 3 and 4 being the most frequent (34.89% each). OM grades 1 and 2 (7.69% and 20.51%, respectively). Similar to oral GVHD, the patient profile was the same regarding sex, mean age, underlying disease, type and source of transplant, compatibility, conditioning regimen, and immunoprophylaxis.

DISCUSSION

HSCT frequently presents oral complications, which can lead to morbidity and increased mortality and have a significant impact on a patient's quality of life[2]. Oral GVHD and OM are two important complications that must be treated to avoid morbidity and impact on patient prognosis.

Several risk factors are associated with the development of oral GVHD including gender, the difference between donor and recipient, especially female donor to a male recipient; advanced age of recipient and donor; primary disease or pre-HSCT comorbidities; the intensity of the conditioning regimen; GVHD prophylaxis protocol used; source of HSC (stem cells mobilized from peripheral blood versus stem cells collected from bone marrow or umbilical cord); type of donor (related or unrelated); and disparity in human leukocyte antigen (HLA) compatibility between donor and recipient[1-6,14,17,18].

The incidence of GVHD is lower after transplants from matched HLA-identical or less-despaired matched donors, compared with non-family or HLA-identical donors. When the conditioning regimen does not include total body irradiation (TCI) or RC RIC and NMA GVHD risk is lower as well as when umbilical cord or bone marrow is used as a source of HSC when compared with peripheral blood[3,4,14,17,18].

Despite prophylaxis with immunosuppressants, on average 50% of patients undergoing allogeneic HSC transplantation may develop GVHD[4,6,7,15,17,18] with varying degrees of severity and mortality that can reach up to 20% of transplanted patients[4]. About 30% to 60% of individuals develop GVHD, with the oral cavity being infrequently affected, and approximately 30% to 80% develop cGVHD, with about 25% to 83% having oral involvement of the disease[1-5,7,14,16,17]. These data corroborate the results obtained in this study, in which 34.04% of the patients developed GVHD and 81.25% with oral manifestations.

As for the conditioning regimen, the most used in the study sample was the MA (80.85%), similar to other studies[1], which is associated with higher toxicity and risk of transplant-related mortality[8,12], as well as with a higher incidence of GVHD compared to RIC and NMA regimens[2,8,9,12,18]. Despite the use of the RC MA in most cases in this study, the small percentage of GVHD can be explained by the fact that the mean age of the sample was 37 years, which is not an age advance. Also, the majority received a related type of transplant (65.95%), fully compatible (55.31%), originating in the bone marrow (74.46%), and used the combination of CSA + MTX as immunosuppressive agents for GVHD prophylaxis in most cases of (85.10%)[1,3-5,14,17,18], corroborating the literature. Studies show that the protocol (CSA + MTX) reduces the onset of acute and chronic GVHD and improves treatment-related mortality after HSCT[4,11,18].

Studies suggest that a mycophenolic acid (MMF) precursor associated with a calcineurin inhibitor (CSA or TCL) is as effective as the combination of MTX and calcineurin inhibitor for the prevention of GVHD, and is also associated with reduced OM and graft improvement[4,5]. Other studies also state that the use of GVHD prophylaxis without MTX is associated with a lower incidence and severity of OM compared with standard or reduced doses of MTX[5,10,25]. Cutler et al. also state that MTX, an antiproliferative prophylactic agent for GVHD, impairs mucosal regeneration after conditioning-related injury, prolonging and worsening mucositis[13]. This combination (CSA + MMF) is generally more used for patients who receive NMA and RIC as CR, while CSA + MTX is the most used prophylaxis in patients who receive a CR MA[4]. In this study, only 14.89% of subjects received CSA + MMF as therapy, and most of these (71.42%) were submitted to RIC or NMA regimens. This low percentage of patients undergoing the CSA + MMF regimen, and the consequent greater use of CSA + MTX, may be associated with the high prevalence of OM (82.97%) in this study.

Regarding the individuals who developed oral GVHD in this study, it might be associated with the fact that, despite the immunoprophylaxis used and the majority receiving the graft from a related, compatible and bone marrow donor, the MA regimen was the most used, which is the CR most associated with the onset of GVHD[2,8,9,12,18]. Another hypothesis would be concerning minor histocompatibility antigens, in which even with identical HLA between patients and donors, many patients still develop GVHD[3].

The intensity of CR also influences the incidence and severity of other complications of allogeneic HSCT, such as OM[10,25], which occurs in approximately 80% of patients undergoing HSC therapy[21,22], as well as in this sample that had 82.97% of patients with OM.

According to Cutler et al., conditioning therapy is the most important cause of OM after allogeneic HSCT[13], with the incidence of OM estimated at 75% to 100% after CR MA[2,25]. We found similar results in this study, with 82.97% of cases of OM, where 87.17% received the MA regimen.

Thus, OM risk factors can be divided into patient-related categories, including age, sex, body mass index, oral environment, genetic predispositions, and treatment, such as RT or QT type, dosage, and schedule[23,25].

Other authors reaffirm these considerations, assuring that the factors that play a significant role in a higher risk of OM are myeloablative therapy and female gender[11,23]. Patients treated with CR MA have a significantly increased risk of OM when compare to those treated with RIC[2,11,18]. Thus, the incidence and frequency of severe OM grades are significantly higher in patients receiving RC MA[10,25], and thus OM is generally less severe, less frequent, and of shorter duration after regimens of RIC and NMA[2,9]. This was confirmed in this study, in which most patients received RC MA and developed more advanced degrees of complication (35.89% had grade 3 and 35.89% had grade 4).

CONCLUSION

Oral GVHD and OM are frequent and debilitating oral complications of HSCT, which in addition to affecting the oral cavity, which can result in discomfort, pain, and impaired function, negatively impacting the quality of life, and can, thus, compromising the general health and survival of the individual. Oral GVHD commonly occurs in elderly individuals who have received an unrelated, incompatible, mobilized peripheral blood donor transplant and who have undergone RC MA. However, the use of immunosuppressive agents, such as CSA + MTX, which is the most used protocol, helps to reduce the prevalence of GVHD. Nonetheless, despite preventing the onset of this condition, immunoprophylaxis for GVHD is associated with a higher incidence and severity of OM, and thus, together with RC MA and the female sex, constitutes an important risk factor for OM. Thus, prevention and early diagnosis for a quick treatment institution are important for a better prognosis. Dentists must be aware of the oral manifestations that may occur after HSCT, and together with the multidisciplinary team, will help to diagnose, treat, and monitor patients who develop post-transplant complications, improving the quality of life of these individuals.

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