Incidence and Clinical Characteristics of Oral Mucositis in Allogeneic Hematopoietic Stem Cell Transplantation with Post-transplant Cyclophosphamide Treatment

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Abstract

Post-transplant cyclophosphamide (PTCy) treatment has been increasingly used in allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, its effects on the burden and severity of oral mucositis (OM) remain unclear. A total of 177 patients received allo-HSCT with PTCy treatment at Xiangya Hospital between 2015 and 2020. Among them, 140 patients whose OM was prospectively graded using the World Health Organization (WHO) oral toxicity scale were included in this retrospective study. The grafts were peripheral stem cells from matched (28/140, 20.0%) and mismatched (112/140, 80.0%) donors. Conditioning intensity was categorized as myeloablative conditioning (MAC; 82/140, 58.6%) or reduced intensity conditioning (RIC; 58/140, 41.4%). The overall incidence of any OM was high (116/140, 82.9%) but the incidence of severe OM was relatively low (40/140, 28.6%). The median duration of OM was 10 days (2–22 days post-transplantation) from day –2 to day +15 (median day +8). Earlier onset of OM was correlated with greater severity. Multivariate analysis showed that conditioning intensity (MAC vs RIC, odds ratio [OR] 6.128, 95% confidence interval [CI] 2.319–16.198) and donor type (mismatched vs matched, OR 3.252, 95% CI 1.089–9.717) were associated with increased risk of severe OM. No significant implications of severe OM were observed on acute or chronic GVHD. Patients with severe OM had slightly worse overall survival, but the difference was not statistically significant ($p = 0.078$). Therefore, severe OM does not appear to lead to a worse transplant outcome if an intensified oral care protocol is adopted.

Introduction

Oral complications following hematopoietic stem cell transplantation (HSCT) typically manifest as a wide range of lesions with varying degrees of severity, ranging from mild, disabling, to life-threatening. Oral mucositis (OM) before trilineage engraftment is one of the most debilitating complications of HSCT. Up to 47–100% of transplant recipients may experience early OM, based on a recent systematic review.[1] OM primarily arises from the direct toxicities of conditioning regimens and a graft-versus-host disease (GVHD) prophylaxis regimen or indirectly from systemic toxicities and the immune status. Furthermore, infections may have a greater contribution to post-transplant OM compared with previous estimations. [2–5]

Post-transplant cyclophosphamide (PTCy), which was initially developed in the setting of haploidentical transplantation[6], has proven to be a promising treatment for transplant recipients with various donor types[7–9], bone marrow or peripheral grafts[8, 10, 11], myeloablative conditioning (MAC) or reduced intensity condition (RIC)[10], and benign or malignant diseases[12–17]. However, the burden and severity of OM remain unclear when a high dose of a cytotoxic drug such as cyclophosphamide is used shortly after the conditioning. To facilitate the management and prevention of OM for transplant recipients receiving PTCy treatment, we performed a retrospective analysis to evaluate the incidence, clinical patterns, risk factors, and clinical significance of OM in a cohort of patients who received allo-HSCT with PTCy treatment.

Patients And Methods

Study design and population

This was a single-center study of patients who presented at the stem cell transplant department of Central South University Xiangya Hospital, Changsha, China, between 2015 and 2020. The patients underwent allogeneic HSCT after providing informed consent. The Institutional Review Board (IRB) approved the study in accordance with the Declaration of Helsinki. Data and associated electronic materials were independently retrospectively reviewed by two researchers. A patient was included if the HSCT platform was based on PTCy treatment and the grade of OM was based on the World Health Organization (WHO) scale. This cohort was not restricted according to transplant indication and donor and conditioning types. All patients received mobilized peripheral blood stem cells. Severe OM was defined as grades 3 to 4.

Transplant protocols

Based on high-resolution typing of class I (A, B, and C) and class II (DR and DQ) human leukocyte antigen (HLA), donors were classified as either matched or mismatched (less than a 10/10 HLA match). Transplantation from mismatched unrelated donors and haploidentical donors was either based on a clinical trial or real-world situation with approval of the clinical IRB. The conditioning regimen was either MAC or RIC defined according to the Bacigalupo criteria.[18] Total body irradiation was not included in our conditioning regimen. Prophylaxis against GVHD was based on a uniform PTCy regimen, combining a high dose of cyclophosphamide with a short course of methotrexate (MTX; 15 mg/m² on days 1 and 10 mg/m² on days 2 and 5) treatment after transplant. Per the institutional protocol, leucovorin was not administered following minimal MTX administration. Cyclosporine A was intravenously administered from day 6 after transplant and switched to oral administration after 3 weeks if the patient was able to take oral medications. In the case of matched or mismatched donors, cyclosporine prophylaxis was administered for 6 or 9 months and subsequently tapered in patients with no active GVHD. Mycophenolate mofetil is not regularly used in our transplant protocol. Rabbit anti-thymocyte globulin (ATG; Genzyme, France) at a total dosage of 8 mg/kg was administered over 4 days to patients with inherited benign disorders such as severe thalassemia.

Prevention and management of mucositis

According to our protocol, an intensive OM care plan was adopted. In the phase prior to conditioning, all patients were advised to consult a dental team for oral examination and elimination of dental, periodontal, endodontic, and oral mucosal lesions or active infections. From the initiation of conditioning therapy, all patients received a prophylaxis regimen including systematic infection prevention for fungi, viruses, and bacteria. Local oral care involved treatment with a nystatin suspension of 4 wU/ml (3 ml) and 0.2% chlorhexidine (5 ml) in addition to basic oral hygiene. The mouthwashes were prescribed to be used every 4 hours. Upon a diagnosis of mucositis, a suspension of granulocyte macrophage-colony

stimulating factor was added to the previous oral care regimen. Opiates were used if necessary, to control the pain associated with mucositis.

Statistical analysis

Comparison of baseline characteristics of patients with and without severe OM was performed using the Chi-square test, Fisher exact test, or Mann-Whitney *U* test. Continuous variables were compared using the non-parametric Kruskal-Wallis test. Multivariate logistic regression analysis was performed to identify independent predictors of mucositis. Transplantation outcomes such as the incidence of acute GVHD (aGVHD), chronic GVHD (cGVHD), and engraftment of donor blood cells were also compared between patients with and without severe OM. Overall survival was estimated using the Kaplan-Meier calculator and compared between groups using the log-rank test. All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA).

Results

Population characteristics

The characteristics of the 140 patients and their donors included in this study are summarized in Table 1. The patients represented a wide age range with a median of 15 years. The indication of HSCT was benign disorders for the majority of patients, including severe aplastic anemia (55, 39.3%), paroxysmal nocturnal hemoglobinuria (PNH) (2, 1.4%), inherited bone marrow failure (2, 1.4%), severe thalassemia (42, 30.0%), inherited immune deficiency (3, 2.1%), and leukodystrophy (3, 2.1%). Among the remaining 34 patients who underwent HSCT for treatment of a malignancy, 10 had acute leukemia (7.1%) and 24 had myelodysplastic syndrome (17.1%). Less than 30% of the donors were matched (13.6% related and 14.3% unrelated), and among the mismatched donors, 65.7% were haploidentical related donors and 6.4% were unrelated donors. With respect to the conditioning regimens, MAC was more frequently used than RIC. Ninety of the 140 (64.3%) transplants included ATG in the GVHD prophylactic regimen along with PTCy.

Table 1
Population characteristics

	Overall	OM Grade 0–2	OM Grade 3–4	P value
Age (median, range)	15 (2–69)	11 (2–69)	23 (3–53)	< 0.001
Gender (count, %)				0.101
Female	55 (39.3)	35 (35.0)	20 (50.0)	
Male	85 (60.7)	65 (65.0)	20 (50.0)	
Diseases (count, %)				< 0.000
Benign	106 (75.7)	87 (87.0)	19 (47.5)	
Malignancy	34 (24.3)	13 (13.0)	21 (52.5)	
Donor type (count, %)				0.012
Matched (MRD, MUD)	39 (27.9)	34 (34.0)	5 (12.5)	
mismatched (HRD, mMUD)	101 (72.1)	66 (66.0)	35 (87.5)	
Donor age (median, range)	31 (9–53)	30 (9–48)	34 (9–53)	0.231
Donor gender (count, %)				0.078
Female	50 (35.7)	35 (35.0)	15 (37.5)	
Male	90 (64.3)	65 (65.0)	25 (62.5)	
Condition intensity (count, %)				0.034
RIC	58 (41.4)	47 (47.0)	11 (27.5)	
MAC	82 (58.6)	53 (53.0)	29 (72.5)	
Including ATG (count, %)				0.014
No	50 (35.7)	42 (42.0)	8 (20.0)	
Yes	90 (64.3)	58 (58.0)	32 (80.0)	
MNC (10^8 /Kg) (median, CI 95%)	13.20 (12.66–14.80)	13.20 (12.4–15.50)	13.16 (10.6–14.80)	0.461
CD34+ (10^6 /Kg) (median, CI 95%)	7.00 (6.19–8.37)	7.19 (6.4–9.30)	6.17 (5.1–7.40)	0.053
CD3+ (10^8 /Kg) (median, CI 95%)	3.37 (3.00–4.09)	3.19 (2.67–3.67)	3.62 (3.18–4.60)	0.341

Overall	OM Grade 0–2	OM Grade 3–4	P value
Abbreviations: ATG, anti-thymocyte globulin; HRD, haploidentical related donors; MAC, myeloablative conditioning; mMUD, mismatched unrelated donors; MNC, mononuclear cells; MRD, matched related donors; MUD, matched unrelated donors; OM, oral mucositis; RIC, reduced intensity conditioning.			

OM characteristics

The incidence of OM of all grades, grades 2–4, and grades 3–4 was 82.9% (116/140), 60% (84/140), and 28.6% (40/140), respectively. The incidence of severe OM in the MAC and RIC groups was 35.4% and 18.9%, respectively. OM occurred at a median of day + 6 (range, day 0 to + 15) (Fig. 1a) after HSCT with a median duration of 7 days (2–22 days) (Fig. 1b). Both early onset and longer duration of OM correlated with its severity (Fig. 1c - d). The time from HSCT to OM was similar between patients in different conditioning regimen groups (MAC vs RIC, median 6 days for both, p = 0.200) and those with underlying diseases (benign vs malignancy, median 6 days for both, p = 0.688). A longer duration of OM was observed in transplant recipients in the MAC group compared with that in the RIC group (median 8 days vs 6 days, p = 0.023) and in recipients with malignancy compared with that in recipients with benign disease (median 10 days vs 6 days, p = 0.001).

Risk factors for OM

Patients who developed severe OM (grades 3–4) were more likely to be older (median 23 vs 11 years old, p < 0.001), have a malignant disorder (52.5% vs 13.0%, p < 0.001), have received MAC (72.5% vs 53%, p = 0.034), and not receive ATG as part of the GVHD prophylaxis regimen (80.0% vs 58.0%, p = 0.014). Other transplant characteristics such as gender of the donors and dose of mononuclear cells (CD34 + and CD3 + cells) were similarly distributed between the two OM groups (Table 1). In multivariate analysis, the conditioning intensity (MAC vs RIC, odds ratio [OR] 6.128, 95% confidence interval [CI] 2.319–16.198) and donor type (mismatched vs matched, OR 3.252, 95% CI 1.089–9.717) were associated with increased risk of severe OM. Inclusion of ATG in the GVHD prophylaxis regimen was associated with reduced risk of severe OM (OR 0.124, 95% CI 0.044–0.351).

Outcomes associated with OM

We did not find an association between severe OM and aGVHD (p = 0.5556), cGVHD (p = 0.798), engraftment of neutrophils (p = 0.509), and engraftment of platelets (p = 0.703). Moreover, there was no significant difference in overall survival according to the severity of OM with a median follow-up of 561 days (95% CI 538–737 days) (Fig. 2).

Discussion

OM is one of the most common complications of HSCT. However, to the best of our knowledge, the incidence and severity of OM among patients with PTCy-based allogeneic HSCT have been unclear to date.[19]

In our cohort of 140 cases who received transplants with PTCy treatment, the incidences of any OM (82.9%) and severe OM (28.6%) were comparable to those in previous reports, in cases using a traditional transplant regimen other than PTCy (47.2–100% and 2.5–60.9%, respectively).[1, 20–25, 19, 26] PTCy-based prophylaxis was reported to show a better safety profile compared with ATG and was associated with reduced severity of mucositis.[27] In our study, more severe OM was observed in patients after an intensive conditioning regimen (MAC) compared with that after a less intensive regimen (RIC). In a recent study using RIC and PTCy, severe OM was observed at a similar frequency (15%) in patients with leukemia or myelodysplastic syndrome.[28] Using the PTCy platform, OM typically began about 1 week after completing the conditioning regimen and lasted for 6–10 days. An early onset of OM would suggest a greater possibility of subsequent severe OM. This information is important for a nursing team to establish a personalized protocol for an oral care regimen.

Because severe OM requires special medical attention such as parenteral nutrition, infection prophylaxis, and fluid replacement, we focused on the risk factors associated with severe OM (above grade 3 according to the WHO criteria) as opposed to cases of mild or moderate OM. MAC was associated with increased risk of severe OM in our cohort, based on both univariate and multivariate analyses. This result was in line with those of previous studies.[19, 29–31] However, the incidence of severe OM in this study was lower than that in previous reports.[1] This might be reflective of the relatively younger patients, more frequent use of fludarabine-based reduced toxicity conditioning regimens,[19] and the standardized and intensified oral care protocol. Notably, mismatched donors and lack of ATG in the GVHD prophylaxis regimen were significantly related to severe OM in multivariate analysis. The underlying reason for these protective effects is currently unclear. Therefore, studies on whether and how the immune status plays a role in the mechanism of early OM post-transplant are warranted.

In line with previous studies, severe OM was not associated with higher incidence of aGVHD and cGVHD. We also did not observe a detrimental influence of severe OM on engraftment of neutrophils and platelets. Although the occurrence of severe OM did not lead to significantly worse overall survival, the clinical implications of severe OM should not be ignored. Indeed, OM has been reported to be the single most debilitating complication of a transplant, causing severe pain, affecting oral function, increasing the risk for bleeding and systemic infection, and having the potential to compromise the upper airway. References are needed to support this statement. Accordingly, oral care was intensively implemented from the beginning of HSCT according to our institutional protocol, including prevention and symptomatic management of OM.

There are several limitations to this study. First, although OM was graded according to the WHO scale, the full picture of oral changes such as the number, location, and stage of the lesions was not systematically recorded and analyzed. Including the specific symptoms and findings from the oral examination may offer a better definition of the mucositis burden and phenotype. Second, although OM was prospectively documented daily following the local protocol, this was not a prospectively designed study. Therefore, the grading of OM would have likely differed according to the individual primary nurses. Finally, this was a single-cohort study, which might have limited the power to detect meaningful associations.

In summary, OM remains a high-burden complication among allogeneic-HSCT recipients receiving PTCy treatment. However, the incidence of severe OM does not appear to be increased on this platform. Patients who receive MAC and cells from a mismatched donor are at greater risk for developing severe OM. ATG included in the GVHD prophylaxis may reduce the risk of severe OM via an as-yet unknown mechanism. The occurrence of severe OM did not lead to a worse transplant outcome if intensified oral care was adopted. Understanding the pathophysiology of OM development could facilitate the development of novel strategies to manage oral complications in allogeneic-HSCT recipients.

Declarations

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The authors declare that they have no conflict of interest.

Ethics approval (include appropriate approvals or waivers):

The HSCT protocols for the treatment were approved by the institutional review board (IRB).

The conduct of this study was approved by the IRB.

Consent to participate (include appropriate statements):

Not applicable

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Availability of data and material (data transparency):

Not applicable

Code availability (software application or custom code):

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Figures

Figure 1

Characteristics of oral mucositis in patients receiving the PTCy platform. Distribution of cases with oral mucositis by onset time (days) (A) and by duration (days) (B). Association between oral mucositis severity (grades 1 to 4) and the onset time (days) (C) and duration (days) (D).

Figure 2

Overall survival according to the severity of oral mucositis.