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Clinical Characteristics of Children and Adolescents Undergoing Hematopoietic Cell Transplant who develop Oral Mucositis

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Abstract

Purpose/Objectives: To describe the clinical characteristics of children and adolescents undergoing hematopoietic cell transplant (HCT) who develop oral mucositis, thus providing preliminary data for the development and implementation of preventative interventions.

Design: Retrospective cohort study

Sample: 45 patients (N= 45) underwent HCT between July 2015 and May 2016

Setting: St. Jude Children's Research Hospital

Methods: Clinical factors were described as transplant type, severity or grade of mucositis, mucositis duration, days to engraftment, total parenteral nutritional support (TPN), use of intravenous (IV) opioid pain management during mucositis, positive blood or oral cultures and length of hospitalization and then compared across mucositis grade.

Results: 24 patients had grade 3 mucositis on-set from day -3 to day 9 of transplant and of these, 23 required IV opioid pain medication to treat mucosal pain. Patients with mucositis grade 3 were more likely to have undergone an allogeneic transplant, receive TPN, have documented positive blood or oral cultures, and longer hospitalizations than those with low-grade mucositis (grade 2).

Conclusions: These findings describe the clinical characteristics between children and adolescents with low and high-grade mucositis and provide timing of mucositis on-set and outcome variables in the development of an intervention to prevent and alleviate pain in children and adolescents at greatest risk for severe mucositis while undergoing HCT.

Implications for nursing: Grade 3 mucositis in children and adolescents undergoing HCT is associated with increased morbidity; therefore, nurses are in a unique position to propose and administer nursing interventions to prevent and alleviate symptoms.

Oral mucositis is an inflammation of the oral mucosa developing from a breakdown in the mucosal tissue, which leaves it open to ulceration and infection. Signs of mucositis include erythema, painful mucous membranes, taste alterations, mouth dryness, ulcerations, and

bleeding. The pain associated with mucositis can lead to difficulty talking and swallowing, ultimately affecting oral intake. Many patients experiencing oral mucositis pain require opioids and in the event of poor intake or malnutrition, parenteral nutrition is required. Oral mucositis has been reported as the single most debilitating side effect in patients undergoing HCT (Bellm, Epstein, Rose-Ped, Martin, & Fuchs, 2000), causing life-threatening complications and ultimately leading to an increase in days of hospitalization and overall cost of treatment (Sonis et al., 2001).

Children and adolescents receiving myeloablative high dose chemotherapy preparation for HCT are at risk for oral mucositis. Soto et al. (2015) reported the incidence of oral mucositis in predominately adult HCT patients ranges between 76% and 89%, but stated that cross-study comparisons can be difficult due to individual differences such as age, diagnoses, and treatment protocol. Bardellini et al. (2013) performed a retrospective study of 55 medical records of children ages two months to 12 years with primary immunodeficiencies who underwent HCT. Oral mucositis developed in 42 patients (76.4%), with seven patients developing grade 3 mucositis (16.7%). The duration of the mucositis was <15 days in 21 cases, from 15 to 36 days in 20 cases, and >36 days in one case. The study also found that an increase in the severity of the preparative regimen before HCT was associated with an increase in oral mucositis incidence ($p<0.01$).

Sonis et al. (2001) evaluated the relationship between oral mucositis and specific clinical outcomes. Ninety-two HCT predominately adult patients from eight centers were included. The peak mucositis severity score correlated with significant infections, total parenteral nutrition (TPN) days, injectable opioid days, total hospital days, and mortality. Additionally, the severity and duration of oral mucositis significantly increased the total cost of care in HCT patients. Further analysis found that the mean hospital charges of patients experiencing mucosal ulceration were \$42,749 higher than those without.

While oral mucositis remains a common toxicity of HCT and results in many complications, preventive interventions that are widely utilized in adults undergoing HCT are considered weak recommendations within the oral care guidelines of the pediatric population (Sung et al., 2017). These recommendations include the initiation of cryotherapy, keratinocyte growth factor and low-level laser therapy during the transplant process (Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology mucositis guidelines, 2014; Sung et al., 2017). Although there have been randomized controlled trials supporting the use of these interventions in the prevention of high-grade oral mucositis during the transplant process, questions about their feasibility, efficacy, and implementation within the pediatric HCT population remain (Sung et al., 2017). Specifically, there are no clear recommendations for when the interventions should be implemented during the transplant process. In order for such interventions to be successful in reducing the incidence and severity of oral mucositis, a clear timeline in which oral mucositis presents itself is necessary.

Thus, the purpose of this retrospective review was to better define treatment parameters through the description of characteristics among children and adolescents experiencing severe oral mucositis, including specific timing of mucositis development, duration of

mucositis and associated clinical factors. Identifying these clinical factors will provide preliminary data for treatment parameters necessary to implement interventions that may alleviate patient pain and suffering.

Methods

Study Design and Data Collection

All patients, ages 2–25 years of age, undergoing an autologous (myeloablative) or allogeneic (myeloablative, radiation) HCT for leukemia or solid tumor between July 2015 and May 2016 were included in this retrospective review and grouped based on mucositis severity (high grade mucositis defined as grade 3 on the Common Terminology Criteria of Adverse Events v. 3). Grading was completed retrospectively by a clinical researcher within the institution based on inpatient notes describing the clinical presentation of oral mucositis. Demographic and clinical data were obtained from electronic medical review and included age, gender, diagnosis, transplant date, and type of transplant (allogeneic vs. autologous). Inpatient notes and labs were investigated further to determine the day of mucositis onset, severity, duration of mucositis, onset of mucositis to day of engraftment, day from engraftment to resolution of mucositis, nutritional support, pain management, and infection. TPN support needed during the mucositis event was based on mucositis grade, predicted duration of mucositis, oral intake, and registered dietician recommendation. Indicators of infection included positive blood or oral cultures during mucositis. Patient records were also reviewed for the administration of IV narcotic pain medications prescribed to treat mucositis pain. The data was then compared with the patients who were without or low-grade oral mucositis (grade 2) during the set period. The study was approved by the Institutional Review Board.

Statistical Analysis

Patients' demographic and clinical characteristics were summarized by descriptive statistics (number and percent, or median and range) for patients with and without mucositis. Demographic and clinical variables were compared between the group with and without mucositis. Moreover, the onset and duration of mucositis was summarized by descriptive statistics, including days from transplant to mucositis, days from start of mucositis to engraftment, and days from engraftment to end of mucositis.

The differences of categorical variables between the two groups were assessed by Fisher's exact tests, and those of the continuous variables were tested by Wilcoxon rank-sum tests. Statistical analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC) and a two-sided significance level of $P < 0.05$ was used for all statistical tests.

Results

Sample Characteristics

45 patient electronic medical records were eligible for this retrospective study. The demographic and clinical data for all patients is displayed in Table 1. The median age was 10 (range 2.1–24.8). Fifty-one percent of the patients were female and 62% were white.

Fifty-eight percent had undergone HCT for Leukemia/Lymphoma and 53% of the transplants were allogeneic.

A total of 24 patients (53%) developed grade 3 oral mucositis during their hospitalization. The clinical characteristics of patients within the mucositis group are described in Table 2. The duration of mucositis was less than 15 days in 71% of the mucositis patients, with a median of 11.5 days duration (range 0 to 47). In days from transplant to the onset of oral mucositis, there was a median of 3.5 days (range –3 to 9), but mucositis occurred as early as day 3 of the conditioning regimen. There was a median of 9 days (range 3 to 26) from the start of oral mucositis to engraftment and a median of 2 days (range –21 to 26) from engraftment to the end of oral mucositis. Seventy-one percent of mucositis patients had positive blood or oral cultures, 96% of mucositis patients were prescribed pain medication for mucosal pain, and 100% received parenteral nutrition.

The demographic and clinical factors were then compared between those without or low-grade oral mucositis (grade 0–2) to those with mucositis (grade 3), while undergoing a HCT. Within the low-grade mucositis cohort, mucositis did not develop in 8 patients (grade 0), 13 patients were classified as grade 1, and only 1 as grade 2. Table 3 compares the demographic and clinical differences between patients with and without mucositis (<grade 2). There were no significant differences in age, gender, and race between the two groups. The median and range of days from transplant to engraftment differed between groups, those without mucositis had a range of 9 to 22 days and a median of 12 days from transplant to engraftment and the days for those with mucositis ranged from 9 to 27 days and a median of 13 days. However, these differences were not significant.

There were significant differences in the diagnosis, type of transplant, positive blood or oral cultures, parenteral nutrition, and length of stay between groups. In those with mucositis, leukemia/lymphoma was the most common diagnosis and they were more likely to have undergone an allogeneic HCT. Seventy-one percent of those with oral mucositis had an allogeneic transplant compared to 33% of those without mucositis ($p=0.017$). The lengths of stay were greater for those with mucositis with a median of 32 days (range 21 to 332), compared to those without mucositis with a median of 23.5 days (range 11–45) ($p=0.002$). Sixty-eight percent of those who had documented blood or oral cultures belonged to the mucositis group ($p=0.038$). Additionally, 63% of the patients who received parenteral nutrition had grade 3 mucositis ($p=0.003$). All patients with grade 1–3 mucositis required IV pain management for mucosal pain.

Discussion

Our findings indicate that the clinical characteristics of oral mucositis are similar to those in adults. Sonis et al. (2001) reported the correlation between mucositis severity and infections, days of nutritional support, and extended hospitalization, which is consistent with our findings. However, we found the need for pain management to be no different between those with low and high-grade mucositis, with all requiring IV opioid support for pain during mucositis. Patients undergoing an allogeneic transplant were at the highest risk for grade 3 mucositis, which occurred as early as day –3 and is supported in the adult literature with

high-grade mucositis being associated with high dose chemotherapy and/or radiation (Bardellini et al., 2013). Lastly, those with high-grade mucositis had a higher incidence of positive blood or oral cultures, parenteral nutrition, as well as longer hospitalizations compared to those with low-grade mucositis.

Descriptions of clinical characteristics of children and adolescents undergoing HCT who develop oral mucositis is limited in the literature, specifically regarding days to mucositis onset, duration and days to engraftment. This information is vital in the implementation of oral mucositis prevention interventions. As described, high-grade mucositis developed from day -3 to day 9 of the transplant trajectory, supporting the need to initiate preventive therapy during the conditioning regimen and continuing after HCT. Additionally, there was a median of 2 days from engraftment to mucositis resolution which also provides evidence to the necessity of continuing prevention interventions post-transplant. Few RCTs testing the efficacy of the clinical practice guidelines supported by MASCC/ISOO (2014) have adhered to this timeline (Sung et al., 2017).

This study provides preliminary data to assist in future protocol development for the prevention and treatment of high-grade oral mucositis. Currently, the MASCC/ISOO clinical practice guidelines for the management of oral mucositis (2015) do not identify recommendations regarding when prevention interventions such as cryotherapy, low level laser therapy, and keratinocyte-growth factor should be implemented and for how long. Therefore, this study will guide preventive intervention initiation on day -1 of the conditioning regimen and continuing until engraftment (absolute neutrophil count >500 for 2 days).

Limitations

Although this study was able to quantify the clinical characteristics children and adolescents undergoing HCT who develop oral mucositis, there were several limitations. The study did not look at specific conditioning regimens and protocols because of the heterogeneity between patients. Since we did not collect specific information about all pain medications prescribed during hospitalization, we could not analyze if the presence of mucositis correlated with an increased need of opioids. Additionally, this study did not analyze the amount of pain medication prescribed according to mucositis grade.

Implications for Nursing: This study provides preliminary data to assist in future protocol development for the prevention and treatment of high-grade oral mucositis and characteristics of those at greatest risk of higher-grade mucositis including transplant regimen and underlying cancer. Implementing preventive interventions in accordance with the timeline in which oral mucositis presents itself may significantly reduce the incidence of oral mucositis in this high-risk patient population, thus improving health-related quality of life, morbidity, and overall health care costs.

Conclusion

Understanding the clinical characteristics of oral mucositis in children and adolescents undergoing HCT is vital in developing new treatment and prevention protocols. Further

research in the pediatric and adolescent HCT population is needed to implement oral mucositis prevention interventions during the proposed timeline.

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Knowledge Translation:

- High-grade oral mucositis affects over half of children and adolescents undergoing HCT.
- High-grade mucositis is associated with children and adolescents diagnosed with leukemia/lymphoma undergoing an allogeneic HCT, with higher needs for nutritional support, higher risk for infection, and longer hospitalization.
- The timeline in which oral mucositis presents itself provides treatment parameters on initiation and discontinuation of preventive interventions during the transplant trajectory.

Table 1.

Characteristics of patients who have undergone HCT (N=45)

	n	%
Age at transplant, years		
Median (Range)	10 (2.1 to 24.8)	
Gender		
Female	23	51
Male	22	49
Race		
White	28	62
Black	10	22
Other	7	16
Diagnosis		
Leukemia/Lymphoma	26	58
Solid Tumor	19	42
Type of transplant		
Allogeneic	24	53
Autologous	21	47
Days from transplant to engraftment, n=44[*]		
Median (Range)	12.5 (9 to 27)	
Days hospitalized		
Median (Range)	30 (11 to 332)	
Documented positive blood or oral cultures		
No	20	44
Yes	25	56
Parenteral nutrition		
No	7	16
Yes	38	84
Developed high grade OM		
No (<Grade 3)	21	47
Yes(>Grade3)	24	53

Abbreviations: HCT, hematopoietic cell transplant;

OM, oral mucositis.

*
One patient died before engraftment.

Table 2.

Characteristics of patients with high grade OM during HCT (N=24)

	n	%
Age at transplant, years		
Median (Range)	12 (2.4 to 19.9)	
Gender		
Female	14	58
Male	10	42
Race		
White	16	67
Black	5	21
Other	3	13
Diagnosis		
Leukemia/Lymphoma	18	75
Solid Tumor	6	25
Type of transplant		
Allogeneic	17	71
Autologous	7	29
Days from transplant to engraftment, n=24[*]		
Median (Range)	13 (9 to 27)	
Days hospitalized		
Median (Range)	32 (21 to 332)	
Severity of OM		
Grade 3	24	100
Duration of OM, days		
<15	17	71
15 to 28	6	25
>28	1	4
Median (Range)	11.5(0 to 47)	
Days from transplant to OM		
Median (Range)	3.5 (-3 to 9)	
Days from start of OM to engraftment, n=24[*]		
Median (Range)	9 (3 to 26)	
Days from engraftment to end of OM, n=24[*]		
Median (Range)	2 (-21 to 26)	
Documented positive blood or oral cultures		
No	7	29
Yes	17	71
Pain medications for OM		
No	1	4
Yes	23	96
Parenteral nutrition		

	n	%
Yes	24	100

Abbreviations: OM, oral mucositis.

* One patient died before engraftment.

Table 3.

Associations between potential risk factors and OM

Developed High Grade OM					
	No(N=21) ^a		Yes (N=24) ^b		
	n	%	n	%	P
Age at transplant, years					
Median (Range)	6.8 (2.1 to 24.8)		12 (2.4 to 19.9)		0.280
Gender					
Female	9	39	14	61	0.376
Male	12	55	10	45	
Race					
White	12	43	16	57	0.761
Black	5	50	5	50	
Other	4	57	3	43	
Diagnosis					
Leukemia/Lymphoma	8	31	18	69	0.017 [*]
Solid Tumor	13	68	6	32	
Type of transplant					
Allogeneic	7	29	17	71	0.017 [*]
Autologous	14	67	7	33	
Days from transplant to engraftment[*]					
Median (Range)	12 (9 to 22)		13 (9 to 27)		0.315
Days hospitalized					
Median (Range)	24 (11 to 45)		32 (21 to 332)		0.002 [*]
Documented positive blood or oral cultures					
No	13	65	7	35	0.038 [*]
Yes	8	32	17	68	
Parenteral nutrition					
No	7	100	0	0	0.003 [*]
Yes	14	37	24	63	

Abbreviations: OM, oral mucositis.

^aIncludes patients that did not develop OM and those that developed OM grades 1 and 2.^bIncludes patients that developed OM grade 3.

* Sample size for patients that developed high grade OM is based on n=23 as one patient died before engraftment.

* Statistically significant, P<0.05