Clinical Characteristics of Children and Adolescents Undergoing Hematopoietic Cell Transplantation Who Develop Oral Mucositis

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OBJECTIVES: To describe the clinical characteristics of children and adolescents undergoing hematopoietic cell transplantation (HCT) who develop oral mucositis.

SAMPLE & SETTING: 45 patients who underwent HCT from July 2015 to May 2016 at St. Jude Children's Research Hospital in Memphis, Tennessee.

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

RESULTS: 24 patients had grade 3 or greater mucositis onset from day –3 to day 9 of transplantation; of these, 23 required IV opioid medication to treat mucosal pain. Patients with mucositis grade 3 or greater were more likely to have undergone an allogeneic transplantation, receive TPN, have documented positive blood or oral cultures, and have longer hospitalizations than those with low-grade mucositis.

IMPLICATIONS FOR NURSING: Nurses are in a unique position to propose and administer interventions to prevent and alleviate symptoms of mucositis.

KEYWORDS children and adolescents; hematopoietic cell transplantation; oral mucositis

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Oral mucositis is an inflammation of the oral mucosa developing from a breakdown in the mucosal tissue; this breakdown 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, total parenteral nutrition (TPN) is required. Oral mucositis has been reported as the single most debilitating side effect in patients undergoing hematopoietic cell transplantation (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 that the incidence of oral mucositis in predominately adult patients undergoing HCT ranges from 76%–89%, but they stated that cross-study comparisons can be difficult because of individual differences, such as age, diagnoses, and treatment protocol. Bardellini et al. (2013) performed a retrospective study of 55 medical records of children aged 2 months to 12 years with primary immunodeficiencies who underwent HCT. Oral mucositis developed in 42 patients, with 7 patients developing grade 3 mucositis. The duration of the mucositis was less than 15 days in 21 cases, 15–36 days in 20 cases, and more than 36 days in one case. Bardellini et al. (2013) 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 predominately adult patients undergoing HCT from eight centers were included. The peak mucositis severity score correlated with significant infections, TPN days, injectable opioid days, total hospital days, and mortality. In addition, the severity and duration of oral mucositis significantly increased the total cost of care in patients undergoing HCT. Further analysis found that the mean hospital charges of patients experiencing mucosal ulceration were $42,749 higher than those without.

Although oral mucositis remains a common toxicity of HCT and results in many complications, preventive interventions that are widely used 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 transplantation process (Lalla et al., 2014; Sung et al., 2017). Although randomized, controlled trials have supported the use of these interventions in the prevention of high-grade oral mucositis during the transplantation process, questions about their feasibility, efficacy, and implementation within the pediatric HCT population remain (Sung et al., 2017). Specifically, no clear recommendations exist for when the interventions should be implemented during the transplantation process. For such interventions to be successful in reducing the incidence and severity of oral mucositis, a clear time line in which oral mucositis presents itself is necessary.

TABLE 1. Characteristics of Patients Who Underwent Hematopoietic Cell Transplantation (N = 45)

Characteristic	n
Gender	
Female	23
Male	22
Race	
White	28
Black	10
Other	7
Diagnosis	
Leukemia or lymphoma	26
Solid tumor	19
Type of transplantation	
Allogeneic	24
Autologous	21
Documented positive blood or oral cultures	
Yes	25
No	20
Total parenteral nutrition	
Yes	38
No	7
Developed high-grade oral mucositis	
Yes (grade 3 or greater)	24
No (less than grade 3)	21

The purpose of this retrospective review is 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, aged 2–25 years, undergoing autologous (myeloablative) or allogeneic (myeloablative, radiation) HCT for leukemia or solid tumor from July 2015 to May 2016 were included in this retrospective review. Patients were grouped based on mucositis severity (high-grade mucositis defined as grade 3 or greater on the Common Terminology Criteria of Adverse Events [National Cancer Institute Cancer Therapy Evaluation Program, 2009]). 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 health record review and included age, gender, diagnosis, transplantation date, and type of transplantation (allogeneic versus autologous). Inpatient notes and laboratory results were investigated further to determine the day of mucositis onset, severity, duration, time from onset to day of engraftment, day from engraftment to resolution, 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 dietitian recommendation. Indicators of infection included positive blood or oral cultures during mucositis. Patient records also were reviewed for the administration of IV narcotic pain medications prescribed to treat mucositis pain. The data then were compared with the patients who were without mucositis or had low-grade oral mucositis (grade 2 or less) during the set period. The study was approved by the St. Jude Children's Research Hospital Institutional Review Board.

Statistical Analysis

Patients' demographic and clinical characteristics were summarized by descriptive statistics for patients with and without mucositis. Demographic and clinical variables were compared between the groups with and without mucositis. In addition, the onset and duration of mucositis were summarized by descriptive statistics, including days from transplantation to start of 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, and a two-sided significance level of $p < 0.05$ was used for all statistical tests.

Results

Sample Characteristics

Forty-five patient electronic health records were eligible for this retrospective study. The demographic and clinical data for all patients are shown in Table 1. The median age at transplantation was 10 years (range = 2.1–24.8 years). Twenty-three patients were female, and 28 were White. Twenty-six patients had undergone HCT for leukemia or lymphoma, and 24 transplantations were allogeneic. The median number of days from transplantation to engraftment was 12.5 (range = 9–27) (n = 44; one patient died before engraftment). The median number of days hospitalized was 30 (range = 11–332).

Twenty-four patients developed grade 3 or greater oral mucositis during hospitalization. The clinical characteristics of patients in the mucositis group are described in Table 2. The duration of mucositis was less than 15 days for 17 patients, with a median duration of 11.5 days (range = 1–47). In days from transplantation to the onset of oral mucositis, the median was 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 = 3–26) 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. Seventeen patients with mucositis had positive blood or oral cultures, 23 were prescribed pain medication for mucosal pain, and all 24 received TPN.

Demographic and clinical factors then were compared between those who had no mucositis (grade 0) or low-grade mucositis (grade 1–2) and those who had grade 3 or greater mucositis while undergoing HCT. In 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

TABLE 2. Characteristics of Patients With High-Grade Oral Mucositis (OM) During Hematopoietic Cell Transplantation (N = 24)

Characteristic	Median	Range
Age at transplantation (years)	12	2.4–19.9
Days from transplantation to engraftment[a]	13	9–27
Days from transplantation to start of OM	3.5	–3 to 9
Days hospitalized	32	21–332
Duration of OM (days)	11.5	1–47
Characteristic		**n**
Gender		
Female		14
Male		10
Race		
White		16
Black		5
Other		3
Diagnosis		
Leukemia or lymphoma		18
Solid tumor		6
Type of transplantation		
Allogeneic		17
Autologous		7
Documented positive blood or oral cultures		
Yes		17
No		7
Total parenteral nutrition		
Yes		24
No		–

[a] One patient died before engraftment (N = 23).

patients with and without mucositis (less than grade 2). No significant differences were found in age, gender, and race between the two groups. The median and range of days from transplantation to engraftment differed between groups; those without mucositis or with low-grade mucositis had a range of 9–22 days and a median of 12 days from transplantation to engraftment, and the days from transplantation to engraftment for those with grade 3 or greater mucositis ranged from 9–27 days, with a median of 13 days. However, these differences were not significant.

Significant differences were found in diagnosis, type of transplantation, positive blood or oral cultures, TPN, and length of stay between groups. In those with grade 3 or greater mucositis, leukemia or lymphoma was the most common diagnosis, and patients with those diagnoses were more likely to have undergone an allogeneic HCT. Seventeen patients with oral mucositis had an allogeneic transplantation, compared to seven patients without mucositis or with low-grade mucositis ($p = 0.017$). The lengths of stay were greater for those with mucositis, with a median of 32 days (range = 21–332), compared to those without mucositis or with low-grade mucositis, with a median of 24 days (range = 11–45) ($p = 0.002$). Seventeen patients in the mucositis group had documented positive blood or oral cultures ($p = 0.038$). In addition, all patients who had grade 3 or greater mucositis received TPN ($p = 0.003$). All patients with mucositis required IV pain management for mucosal pain.

Discussion

The researchers' findings indicate that the clinical characteristics of oral mucositis are similar to those

TABLE 3. Associations Between Potential Risk Factors and Oral Mucositis (OM)

	Developed Grade 3 OM (N = 24)		Developed No or Grade 1 or 2 OM (N = 21)		
Characteristic	**Median**	**Range**	**Median**	**Range**	**p**
Age at transplantation (years)	12	2.4–19.9	6.8	2.1–24.8	0.28
Days from transplantation to engraftment (N = 23)	13	9–27	12	9–22	0.315
Days hospitalized	32	21–332	24	11–45	0.002
Characteristic		**n**		**n**	**p**
Gender					0.376
Female		14		9	
Male		10		12	
Race					0.761
White		16		12	
Black		5		5	
Other		3		4	
Diagnosis					0.017
Leukemia or lymphoma		18		8	
Solid tumor		6		13	
Type of transplantation					0.017
Allogeneic		17		7	
Autologous		7		14	
Documented positive blood or oral cultures					0.038
Yes		17		8	
No		7		13	
Total parenteral nutrition					0.003
Yes		24		14	
No		–		7	

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 the current findings. However, the current researchers 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 transplantation were at the highest risk for grade 3 or greater mucositis, which occurred as early as day –3; this is supported in the adult literature, with high-grade mucositis being associated with high-dose chemotherapy or radiation (Bardellini et al., 2013). In addition, those with high-grade mucositis had a higher incidence of positive blood or oral cultures and TPN, and longer hospitalizations compared to those with low-grade mucositis.

Descriptions of clinical characteristics of children and adolescents undergoing HCT who develop oral mucositis are 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 transplantation trajectory, supporting the need to initiate preventive therapy during the conditioning regimen and continuing after HCT. In addition, the median time from engraftment to mucositis resolution was two days, which also provides evidence of the necessity of continuing prevention interventions post-transplantation. Few randomized, controlled trials testing the efficacy of the clinical practice guidelines supported by the Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Oral Oncology (ISOO) (Lalla et al., 2014) have adhered to this time line (Sung et al., 2017).

The MASCC/ISOO clinical practice guidelines for the management of oral mucositis (Lalla et al., 2014) 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, the current study will guide preventive intervention initiation on day –1 of the conditioning regimen and continuing until engraftment (absolute neutrophil count greater than 500 for two days).

Limitations

Although the current study was able to quantify the clinical characteristics of children, adolescents, and young adults who are undergoing HCT and develop oral mucositis, the study had several limitations. The researchers did not look at specific conditioning regimens and protocols because of the heterogeneity among patients. Because the researchers did not collect specific information about all pain medications prescribed during hospitalization, they could not analyze whether the presence of mucositis correlated with an increased need for opioids. In addition, the researchers did not analyze the amount of pain medication prescribed according to mucositis grade.

KNOWLEDGE TRANSLATION

- High-grade oral mucositis affects more than half of children and adolescents undergoing hematopoietic cell transplantation (HCT).
- High-grade mucositis is associated with children and adolescents diagnosed with leukemia or lymphoma undergoing allogeneic HCT, with greater 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 transplantation trajectory.

Implications for Nursing

The current 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 for higher-grade mucositis, including transplantation regimen and underlying cancer. Implementing preventive interventions in accordance with the time line in which oral mucositis presents itself may significantly reduce the incidence of oral mucositis in this high-risk patient population, thereby improving health-related quality of life, morbidity, and overall healthcare 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 time line.

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Mandrell contributed to the conceptualization and design. Donohoe, Bosi, and Mandrell completed the data collection. Sykes, Lu, and Mandrell provided the statistical support. Donohoe, Sykes, Lu, and Mandrell provided the analysis. All authors contributed to the manuscript preparation.

REFERENCES

Bardellini, E., Schumacher, F., Conti, G., Porta, F., Campus, G., & Majorana, A. (2013). Risk factors for oral mucositis in children receiving hematopoietic cell transplantation for primary immunodeficiencies: A retrospective study. *Pediatric Transplantation, 17,* 492–497. https://doi.org/10.1111/petr.12094

Bellm, L.A., Epstein, J.B., Rose-Ped, A., Martin, P., & Fuchs, H.J. (2000). Patient reports of complications of bone marrow transplantation. *Supportive Care in Cancer, 8,* 33–39.

Lalla, R.V., Bowen, J., Barasch, A., Elting, L., Epstein, J., Keefe, D.M., . . . Elad, S. (2014). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer, 120,* 1453–1461. https://doi.org/10.1002/cncr.28592

National Cancer Institute Cancer Therapy Evaluation Program. (2009). *Common Terminology Criteria for Adverse Events* [v.3.0]. Retrieved from https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf

Sonis, S.T., Oster, G., Fuchs, H., Bellm, L., Bradford, W.Z., Edelsberg, J., . . . Horowitz, M. (2001). Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *Journal of Clinical Oncology, 19,* 2201–2205. https://doi.org/10.1200/JCO.2001.19.8.2201

Soto, M., Lalla, R.V., Gouveia, R.V., Zecchin, V.G., Seber, A., & Lopes, N.N. (2015). Pilot study on the efficacy of combined intraoral and extraoral low-level laser therapy for prevention of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation. *Photomedicine and Laser Surgery, 33,* 540–546. https://doi.org/10.1089/pho.2015.3954

Sung, L., Robinson, P., Treister, N., Baggott, T., Gibson, P., Tissing, W., . . . Dupuis, L.L. (2017). Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation. *BMJ Supportive and Palliative Care, 7,* 7–16.