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Observation Of Outcome Of Oral Mucosal Lesion On Chemotherapy In Children With Acute Lymphoblastic Leukemia

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Abstract

Introduction: *Acute Lymphoblastic Leukemia (ALL) is the most common pediatric malignancy, presenting unique challenges in treatment and management. This study aims to analyze the demographic characteristics, treatment adherence, and incidence of oral mucositis in pediatric ALL patients undergoing chemotherapy.*

Methods: *This prospective observational study included 74 pediatric patients diagnosed with ALL at a specialized center. Data on demographic characteristics, chemotherapy phase completion, and episodes of oral mucositis were collected. The chemotherapy regimen followed the UKALL 2003 protocol, and the World Health Organization mucositis scoring system was used for assessment.*

Result: *The study cohort predominantly consisted of younger children (<5 years: 56.76%) and males (68.92%). The majority had an initial WBC count <50000 per cumm (72.97%). All patients completed the induction phase, but completion rates decreased in subsequent phases. Oral mucositis was observed in 44.59% of patients, with the highest frequency during the induction phase (28.38%). Comorbidities associated with oral mucositis decreased in later phases. The survival rate was high (93.94%), despite the presence of oral mucositis and comorbidities.*

Conclusion: *The study highlights the challenges in maintaining treatment adherence and managing complications like oral mucositis in pediatric ALL. The high survival rate indicates the effectiveness of current treatment protocols and supportive care strategies, emphasizing the need for personalized treatment approaches and comprehensive care.*

Keywords: *Pediatric Acute Lymphoblastic Leukemia, Chemotherapy, Oral Mucositis, Treatment Adherence, Pediatric Oncology*

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I. INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common pediatric malignancy, accounting for 25%-30% of all childhood cancers and about 75% of leukemia cases in children (1). Locally, ALL represents 58% of childhood malignancies in Bangladesh(2). Despite an overall cure rate of 80%, reflecting significant advancements, ALL treatment continues to pose substantial morbidity challenges (3). Chemotherapy, alongside stem cell transplantation, remains the cornerstone of ALL treatment, typically involving phases like induction,

consolidation, CNS directed therapy, and maintenance (4). Among the complications, mucositis, particularly oral mucositis (OM), emerges as a predominant concern in pediatric patients undergoing ALL chemotherapeutic treatment (5–9). Oral mucositis, characterized by inflammation of the oral cavity, is a complex pathological process, intricately linked with pro-inflammatory cytokines and micro-vascular injury to the basal epithelial cells during chemotherapy (10). This process leads to ulcer formation, creating a conducive environment for secondary infections. Clinically, OM presents as erythema, edema, burning sensations, and painful ulcers, significantly affecting patients' ability to swallow, thereby leading to malnutrition and dehydration, which are critical in mucosal regeneration (8). The incidence of oral mucositis in pediatric and adolescent patients undergoing standard-dose chemotherapy and hematopoietic stem cell transplant conditioning treatment is alarmingly high, affecting 40–50% and over 60% of patients, respectively (11–15). Furthermore, oral mucositis leads to serious clinical outcomes like compromised oral intake, weight loss, nutritional deficiencies, and increased healthcare costs (16–18). Complications are exacerbated when oral mucositis is accompanied by localized or disseminated infections due to the immunocompromised state of patients and ulcerative mucosal tissues. This can lead to severe consequences, including delays in treatment or reductions in chemotherapy dosages, directly impacting patient survival (8,18,19).Despite its significance, the impact of oral mucositis on clinical outcomes in pediatric and adolescent populations remains under-studied, particularly in the context of Bangladesh (20). This research aims to address this gap by defining the frequency, range of outcomes, and risk factors of oral mucositis in childhood ALL. The study's findings could be pivotal in developing treatment strategies to prevent or treat oral mucositis, potentially reducing morbidity and mortality in children with ALL. Thus, this study serves an essential purpose in evaluating the frequency, risk factors, and outcomes of oral mucosal lesions in pediatric ALL patients undergoing chemotherapy. While there is a growing body of literature on the subject, there remains a significant gap in understanding the specific implications of oral mucosal lesions in pediatric ALL patients. Studies have primarily focused on the broader aspects of chemotherapy-induced complications, with less emphasis on the nuanced impacts of oral lesions (21,22). Furthermore, the role of adherence to oral chemotherapy and its relationship with the development of oral complications is not well-explored (23,24). This study aims to delve deeper into the observation of oral mucosal lesions in pediatric ALL patients, focusing on their frequency, risk factors, and outcomes. Understanding these aspects is crucial for developing targeted interventions to improve patient care and inform treatment protocols. The study's findings could offer valuable insights into enhancing the quality of life and treatment efficacy for these young patients. The primary objective is to observe and analyze the occurrence and progression of oral mucosal lesions in pediatric patients undergoing chemotherapy for ALL. Secondary objectives include identifying potential risk factors and assessing the impact of these lesions on treatment adherence and patient outcomes. Adopting an observational approach, this study aims to provide real-world insights into the management and outcomes of oral mucosal lesions in pediatric ALL patients. Such an approach is pivotal in understanding the day-to-day challenges faced by these patients and in shaping patient-centric care strategies.

II. METHODS

This prospective observational study, conducted from April 2017 to March 2018 at the Department of Pediatric Hematology and Oncology, BSMMU, focused on newly diagnosed children with ALL, aged 1 to 18 years. Initially, 90 patients were selected, but the final sample included 74 cases after accounting for 4 lost to follow-up and 12 who died before completing the induction phase. Inclusion criteria encompassed patients aged 1 to 17.9 years, newly diagnosed with ALL, and those who completed at least the induction remission phase. Exclusion criteria were patients younger than 1 year or older than 18, known cases of oral mucositis, and relapsed cases of ALL. Participant selection was done through consecutive sampling. Data collection involved a pre-tested data sheet, capturing demographic details, clinical history, physical examination, CBC with PBF, and bone marrow studies. Initial laboratory data such as WBC count, ANC, SGPT, and serum creatinine were also recorded. Chemotherapy was administered according to the UKALL 2003 protocol. Patients aged 1 to 9.9 years with an initial WBC count of less than 50000/cumm were considered standard risk and received Regimen-A, which included oral dexamethasone, vincristine, L-asparaginase, 6-mercaptopurine, IT/TIT (intrathecal methotrexate, hydrocortisone, and/or cytosine-arabinoside), oral methotrexate, doxorubicin, cyclophosphamide, and cytosine arabinoside. Patients aged ≥10 years or with an initial WBC count ≥50000/cumm, considered intermediate risk, received Regimen-B, which additionally included daunorubicin. Supportive care like hydration, alkalinization, allopurinol, phosphate binders, and oral and anal care were provided to all patients. Oral mucositis was assessed weekly using artificial white light and the WHO mucositis scoring system. Clinical outcomes measured included comorbidities, recovery time from oral mucositis, and the use of antibiotics, antifungals, and antivirals. Statistical analysis was performed using SPSS version 22.0. Descriptive statistics were calculated for all variables, and associations were analyzed with a p-value <0.05 considered significant. Ethical approval was obtained from the Institutional Review Board of BSMMU, Dhaka. Informed consent was

taken from parents or legal guardians, with the assurance of no harm or treatment delay for the patients. Participants could withdraw from the study at any time without any incentive.

III. RESULTS

Table 1: Distribution of participants by baseline characteristics (N=74)

Variables	Frequency (n)	Percentage (%)
Age group (in years)		
< 5	42	56.76%
5-10	26	35.14%
> 10	6	8.11%
Sex		
Male	51	68.92%
Female	23	31.08%
Initial WBC count (per cumm)		
<50000	54	72.97%
>50000	20	27.03%
Initial ANC (per cumm)		
<500	21	28.38%
>500	53	71.62%
Initial SGPT (U/L) level		
<40	50	67.57%
>40	24	32.43%
Initial serum creatinine (mg/dl)		
<0.30	3	4.05%
0.30-0.70	65	87.84%
>0.70	6	8.11%
Type of ALL		
B-cell type	67	90.54%
T-cell type	7	9.46%
Chemotherapy regimen		
Regimen-A	52	70.27%
Regimen-B	22	29.73%

In this study, a total of 74 pediatric patients diagnosed with Acute Lymphoblastic Leukemia (ALL) were analyzed. The distribution of participants by baseline characteristics revealed a predominance of younger children, with 42 (56.76%) being under 5 years of age, 26 (35.14%) between 5 and 10 years, and only 6 (8.11%) older than 10 years. The cohort had a higher representation of males, with 51 (68.92%) male patients compared to 23 (31.08%) female patients. Regarding the initial white blood cell (WBC) count, a majority of the patients, 54 (72.97%), had a count of less than 50,000 per cumm, while 20 (27.03%) presented with a count exceeding 50,000 per cumm. The initial absolute neutrophil count (ANC) was less than 500 per cumm in 21 (28.38%) patients, whereas 53 (71.62%) had an ANC greater than 500 per cumm. In terms of liver function, as indicated by the initial serum glutamic pyruvic transaminase (SGPT) levels, 50 (67.57%) patients had levels below 40 U/L, and 24 (32.43%) had levels above 40 U/L. The initial serum creatinine levels were predominantly within the normal range, with 65 (87.84%) patients having levels between 0.30 to 0.70 mg/dl, 6 (8.11%) above 0.70 mg/dl, and only 3 (4.05%) below 0.30 mg/dl. The majority of the patients were diagnosed with B-cell type ALL, accounting for 67 (90.54%) of the cases, while T-cell type ALL was observed in 7 (9.46%) patients. Regarding the chemotherapy regimen, 52 (70.27%) patients were treated with Regimen-A, and 22 (29.73%) received Regimen-B.

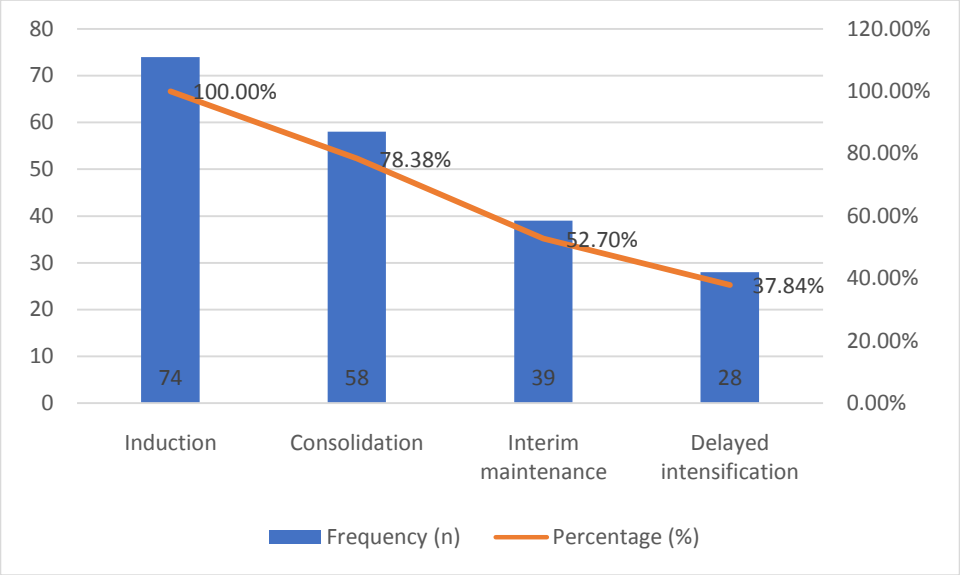

Figure 1: Distribution of participants by completion of chemotherapy phase (N=74)

The progression of the 74 pediatric patients through the various phases of chemotherapy treatment for Acute Lymphoblastic Leukemia (ALL) is depicted in Figure 1. All participants (100%, n=74) successfully completed the Induction phase of their treatment. However, as the treatment progressed through subsequent phases, a decrease in the number of patients completing each phase was observed. In the Consolidation phase, 58 out of the 74 patients (78.38%) completed this stage of treatment. The number further declined in the Interim Maintenance phase, with only 39 patients (52.70%) reaching this stage. The most significant drop was seen in the Delayed Intensification phase, where just 28 patients (37.84%) were able to complete it.

Table 2: Distribution of frequency of episodes of oral mucositis according to completion of chemotherapy phase (N=74)

Chemotherapy phase	(n)	Frequency	Percentage (%)
Induction	74	21	28.38%
Consolidation	58	22	37.93%
Interim maintenance	39	16	41.03%
Delayed intensification	28	15	53.57%

Table 2 illustrates the frequency of episodes of oral mucositis among the 74 pediatric patients at different phases of chemotherapy treatment for Acute Lymphoblastic Leukemia (ALL). The occurrence of oral mucositis varied across the chemotherapy phases, with an increasing trend observed as the treatment progressed. During the Induction phase, 21 out of the 74 patients (28.38%) experienced episodes of oral mucositis. As the patients moved to the Consolidation phase, the frequency of oral mucositis slightly increased, with 22 out of the 58 patients (37.93%) who completed this phase experiencing mucositis. The Interim Maintenance phase saw a further increase in the frequency, with 16 out of the 39 patients (41.03%) reporting episodes of oral mucositis. The highest frequency was observed during the Delayed Intensification phase, where 15 out of the 28 patients (53.57%) who reached this stage experienced oral mucositis.

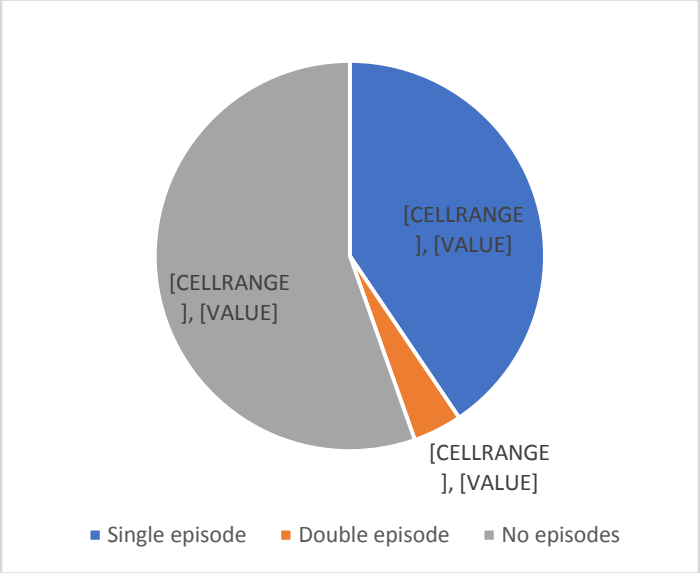

Figure 2: Distribution of episodes of oral mucositis among the participants (N=74)

Out of the total cohort, 41 patients (55.41%) did not experience any episodes of oral mucositis throughout their treatment. However, a significant proportion of the patients did encounter this complication. Specifically, 30 patients (40.54%) had a single episode of oral mucositis. Notably, a smaller subset, comprising 3 patients (4.05%), experienced oral mucositis on two separate occasions. In total, the study recorded 36 episodes of oral mucositis, with the majority being single-episode occurrences.

Table 3: Distribution of episodes of oral mucositis in different phases of chemotherapy (n=36)

Chemotherapy Phase	Frequency	Percentage (%)
Induction	21	58.33%
Consolidation	8	22.22%
Interim maintenance	4	11.11%
Delayed intensification	3	8.33%

The highest frequency of oral mucositis episodes was observed during the Induction phase, with 21 out of the 36 episodes (58.33%) occurring in this initial stage of treatment. As the patients progressed to the Consolidation phase, the frequency of mucositis episodes decreased, accounting for 8 episodes (22.22%). In the subsequent Interim Maintenance phase, the frequency further declined, with 4 episodes (11.11%) being recorded. The Delayed Intensification phase had the lowest frequency of oral mucositis episodes, with only 3 occurrences (8.33%).

Table 4: Distribution of comorbidity with episodes of oral mucositis in different phases of chemotherapy (n=36)

Chemotherapy Phase	Frequency	Percentage (%)
Induction	11	30.56%
Consolidation	4	11.11%
Interim maintenance	2	5.56%
Delayed intensification	3	8.33%

During the Induction phase, comorbidities were observed in conjunction with 11 out of the 36 episodes of oral mucositis, representing 30.56% of the cases. This was the highest frequency of comorbidity observed in any phase. In the Consolidation phase, the frequency decreased, with comorbidities accompanying 4 episodes (11.11%). The Interim Maintenance phase saw a further reduction in comorbidity frequency, with only 2

episodes (5.56%) associated with additional health complications. Similarly, in the Delayed Intensification phase, comorbidities were present in 3 episodes (8.33%) of oral mucositis.

Table 5: Distribution of episodes of oral mucositis as per requirement of treatment (n=36)

Requirement	Frequency	Percentage (%)
Treatment required	27	75.00%
No treatment required	9	25.00%

Out of the 36 episodes of oral mucositis, a majority, 27 episodes (75.00%), necessitated further treatment. This indicates that in most cases, the severity or complications of oral mucositis were such that additional medical intervention was required to manage the condition. On the other hand, 9 episodes (25.00%) of oral mucositis did not require any additional treatment, suggesting that these instances were either of a milder nature or self-resolving without the need for further medical intervention.

Table 6: Distribution of the study patients with oral mucositis associated comorbidities according to clinical outcome (n=33)

Clinical outcome	Frequency	Percentage (%)
Alive	31	93.94%
Death	2	6.06%

Among the patients who developed oral mucositis with comorbidities, a significant majority, 31 out of 33 (93.94%), were alive at the conclusion of the study period. This high survival rate indicates that despite the challenges posed by oral mucositis and accompanying health complications, effective management and treatment strategies were likely in place, contributing to the favorable outcomes for these patients. In contrast, 2 patients (6.06%) succumbed to their conditions. This mortality rate, although relatively low, underscores the potential severity and impact of oral mucositis with comorbidities in pediatric ALL patients.

IV. DISCUSSION

In this study, the demographic distribution of pediatric ALL patients showed a notable predominance of younger children (56.76% under 5 years) and a higher male representation (68.92%), aligning with global pediatric ALL demographics (Ribeiro et al., 2017). The majority of patients presented with an initial WBC count below 50000 per cumm (72.97%), and a significant proportion had an initial ANC above 500 per cumm (71.62%), reflecting typical clinical presentations in ALL (25). The prevalence of B-cell type ALL in our cohort (90.54%) corroborates with the established epidemiological trend that identifies B-cell lineage as the most common in pediatric ALL cases (26).The completion rates across chemotherapy phases in our study, with 100% completing Induction and a gradual decrease in subsequent phases (78.38% in Consolidation, 52.70% in Interim Maintenance, and 37.84% in Delayed Intensification), underscore the challenges in maintaining treatment adherence, a critical factor for successful outcomes, as emphasized by Zeng et al. (21). The observed frequency of oral mucositis episodes, peaking during the Delayed Intensification phase (53.57%), suggests a cumulative toxic effect of chemotherapy on the oral mucosa, a finding that resonates with the study by Proc et al. (2020), which noted immunological changes in the oral cavity during chemotherapy(27).The variability in the incidence of oral mucositis, with 40.54% experiencing a single episode and 4.05% experiencing double episodes, while 55.41% had no episodes, indicates individual differences in susceptibility, potentially influenced by genetic, oral hygiene, and chemotherapy regimen factors (28). The decreasing trend in comorbidity frequency with oral mucositis episodes from Induction (30.56%) to later phases highlights the importance of early phase monitoring and management.

The requirement for additional treatment in 75% of oral mucositis episodes in our study reflects the clinical significance of this complication and the necessity for effective management strategies, as demonstrated in studies by Pourdeghatkar et al. (29). The high survival rate (93.94%) despite the presence of oral mucositis and comorbidities is indicative of effective management strategies, yet the mortality rate of 6.06% underscores the potential severity of these complications, as also noted in the complex case reported by Quirós-Mata et al. (30).

The observation that initial SGPT levels were predominantly below 40 U/L (67.57%) and serum creatinine levels were mostly within the normal range (0.30-0.70 mg/dl in 87.84%) suggests that liver and kidney functions were largely preserved at the onset of treatment, which is crucial for chemotherapy tolerability and dosing.

In summary, our findings provide a comprehensive insight into the clinical course and management challenges in pediatric ALL, particularly regarding the prevalence and impact of oral mucositis. The comparative analysis with existing literature underscores the importance of personalized care strategies, vigilant monitoring, and proactive management to optimize treatment outcomes in this vulnerable patient population.

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

V. CONCLUSION

Our study on pediatric Acute Lymphoblastic Leukemia (ALL) provides critical insights into the demographic characteristics, treatment adherence, and complications associated with chemotherapy, particularly oral mucositis. The predominance of younger children, especially males, in our cohort reflects the demographic trends observed in pediatric ALL globally. The high completion rate of the induction phase and the gradual decrease in completion rates of subsequent chemotherapy phases underscore the challenges in maintaining treatment adherence, a crucial determinant of successful outcomes. A significant finding of our study is the variable incidence of oral mucositis across different chemotherapy phases, with the highest frequency observed during the induction phase. This highlights the need for early intervention and continuous monitoring to manage this complication effectively. The fact that a substantial proportion of oral mucositis episodes required additional treatment emphasizes the clinical significance of this complication and the necessity for effective management strategies. Furthermore, the high survival rate observed in our study, despite the presence of oral mucositis and comorbidities, is indicative of the effectiveness of current treatment protocols and supportive care strategies. However, the mortality rate, although relatively low, underscores the potential severity of these complications and the importance of personalized care strategies. In conclusion, our study contributes valuable data to the existing body of knowledge on pediatric ALL, emphasizing the importance of vigilant monitoring, proactive management of complications like oral mucositis, and adherence to treatment protocols. These findings underscore the need for personalized treatment approaches and highlight the importance of comprehensive care in improving treatment outcomes for pediatric ALL patients.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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