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Side Effects Profile of Chemotherapy in Pediatric Leukemia: A CTCAE v5-Based Study

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Abstract

Background: Treatment with chemotherapy markedly enhance remission rate in pediatrics leukemia. However, it is associated with various side effects (SEs) that can adversely affect the physical, emotional, and social well-being of pediatric patients. This study aims to assess the frequency and severity of chemotherapy-related SEs in pediatric leukemia patients at Benghazi Children's Hospital, Libya. Methods: A descriptive cross-sectional study was conducted from March to September 2023, involving 34 patients aged ≤12 years diagnosed with leukemia and receiving chemotherapy. Data were collected retrospectively from medical records, focusing on demographics, chemotherapy regimens, SEs, and laboratory results. The severity of SEs was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Results: Among the 34 patients, 55.9% were female, with a mean age of 5.9±3.1 years. Acute Lymphoblastic Leukemia (ALL) was diagnosed in 68% of cases. A total of 108 SEs were reported, averaging 3.17 episodes per patient. Neutropenia (21.3%) was the most common SE, followed by nausea and vomiting (12.0%). Severity assessment revealed that 48.1% of SEs were severe, and 22.2% were life-threatening. Conclusion: The study highlights the significant frequency and severity of chemotherapy-related SEs in pediatric leukemia patients, emphasizing the need for tailored monitoring and interventions to improve patient outcomes. Further research is warranted to develop effective preventive strategies.

Keywords: Childhood leukemia, chemotherapy, pediatric patients, Common Terminology Criteria for Adverse Events.

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الملامح العامة للأعراض الجانبية المصاحبة للعلاج الكيميائي في سرطان دم الأطفال: دراسة قائمة على معايير التصنيف الموحد للأثار السلبية السريرية النسخة الخامسة

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الملخص

الخلفية: يعزز العلاج الكيميائي بشكل ملحوظ معدل الشفاء في سرطان الدم لدى الأطفال. ومع ذلك، فإنه مرتبط بآثار جانبية مختلفة يمكن أن تؤثر سلبًا على الرفاهية الجسدية والعاطفية والاجتماعية للمرضى الأطفال. تهدف هذه الدراسة إلى تقييم تكرار وشدة الآثار الجانبية المتعلقة بالعلاج الكيميائي لدى مرضى اللوكيميا الأطفال في مستشفى الأطفال ببنغازي، ليبيا. الطرق: تم إجراء دراسة وصفية مقطعية من مارس إلى سبتمبر 2023، شملت 34 مريضًا تتراوح أعمارهم بين 12 عامًا أو أقل تم تشخيصهم بسرطان الدم ويتلقون العلاج الكيميائي. جمعت البيانات بأثر رجعي من السجلات الطبية. النتائج: من بين 34 مريضًا، كانت 55.9% إناثًا، بمتوسط عمر يبلغ 5.9±3.1 سنوات. تم تشخيص اللوكيميا اللمفاوية الحادة في 68% من الحالات. تم الإبلاغ عن إجمالي 108 حالات طبية طارئة، بمتوسط 3.17 حالة لكل مريض. نقص العدلات (21.3%) هو الأكثر شيوعًا، يليه الغثيان والقيء (12.0%). أظهر تقييم الشدة أن 48.1% من الآثار الجانبية كانت شديدة، و22.2% كانت تهدد الحياة. الخاتمة: تسلط الدراسة الضوء على التكرار الكبير وشدة الآثار الجانبية المتعلقة بالعلاج الكيميائي في مرضى اللوكيميا الأطفال، مما يبرز الحاجة إلى مراقبة وتدخلات مخصصة لتحسين نتائج المرضى. تستدعي الحاجة إلى مزيد من البحث لتطوير استراتيجيات وقائية فعالة.

الكلمات المفتاحية: سرطان الدم في الطفولة، العلاج الكيميائي، المرضى الأطفال معايير المصطلحات الشائعة للأحداث الضارة.

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Introduction

Chemotherapy is a cornerstone in the management of childhood leukemia, a malignancy affecting the blood and bone marrow. This treatment has transformed outcomes, achieving high remission rates for many patients. It is particularly effective for acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML), the most common pediatric cancer (Pui, 1995). However, chemotherapy's benefits are tempered by significant drawbacks. The drugs used can lead to a range of side effects (SEs). These SEs often impact the physical health of young patients. They can also affect emotional and social well-being (Krishnarajan et al., 2021). Common SEs include nausea, vomiting, fatigue, and infections. Severe SEs, such as organ toxicity, can also occur. These side effects may reduce treatment adherence. They can also compromise quality of life (Boogaard et al., 2022). Several factors contribute to the occurrence of SEs in pediatric leukemia patients. The type of chemotherapy drug is a key determinant. For instance, agents like methotrexate are linked to specific toxicities, including bone marrow suppression, mucosal skin lesions, and acute kidney injuries (Mandal et al., 2020). The treatment regimen, including drug combinations, plays a role. The number of chemotherapy cycles influences SEs frequency. Dosage levels are another critical factor. The duration of drug administration can exacerbate side effects, and administration practices, such as infusion timing, also affect outcomes (Slevin et al., 1990). Understanding the frequency of SEs is vital for optimising therapy. Assessing their severity helps tailor supportive care and preventive measures to mitigate the burden of toxicity. This study focuses on pediatric leukemia patients at Benghazi Children's Hospital, Libya. It aims to examine the frequency and severity of chemotherapy-related SEs. A descriptive cross-sectional case study design will be used, this approach enables detailed data collection on SEs characteristics. The findings will highlight the most common SEs in this population. These insights will guide the development of targeted interventions, and improved monitoring and care strategies will enhance outcomes and quality of life for these young patients.

Methods

Study Design: a descriptive cross-sectional design to assess the frequency and severity of chemotherapy-related SEs in leukemia patients at Benghazi Children's Hospital, Libya. This design allows

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for the collection of data from a pediatric population and provides a snapshot of the frequency and severity of SEs in this patient group.

Study Duration: The study was conducted at Benghazi Children's Hospital, Benghazi, Libya from March 2023 to September 2023. It focused on patients ≤12 years old who had been diagnosed with leukemia and are receiving chemotherapy treatment. These patients represent the target population for this research, and their medical records would be collected and analyzed to assess the frequency and severity of chemotherapy-related SEs.

Study Population: All eligible leukemia patients ≤ 12 years old will be considered for inclusion in the study. Inclusion Criteria: Participants who meet the following criteria will be included in the study: (1) age under 12 years old, (2) confirmed diagnosis of leukemia, and (3) receiving chemotherapy treatment at admission. Exclusion Criteria: Participants will be excluded from the study if they do not meet the inclusion criteria, have incomplete medical records or if they have received chemotherapy treatment elsewhere and their records are not accessible.

Sample Size: 34 patients ≤ 12 years old diagnosed with leukemia. Since the aim of the study is to assess the frequency and severity of chemotherapy-related SEs, the focus will be on including all eligible patients within the given time frame to ensure a representative sample size.

Data Collection: Data will be collected retrospectively using data extraction form. The sources of data will be medical records of leukemia patients. These records will contain detailed information regarding patient demographics, chemotherapy regimens, chemotherapy-related SEs, and laboratory test results. Severity levels will be assessed based on Common Terminology Criteria for Adverse Events, Version 5 (CTCAE) to provide a standardized assessment of the severity of SEs.

Data Analysis: Descriptive statistics will be employed to summarize 34 patients' collected data, which will then be subjected to statistical analysis using Microsoft Excel 2010. The data will be presented as frequencies, percentages, ratios, and means ± standard deviations (Confidence Interval CI 95%). The results of the data analysis will be presented in a clear and concise manner, using tables, graphs, and charts. These findings will contribute to a comprehensive

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understanding of the frequency and severity of chemotherapy-related SEs in leukemia patients.

Ethical Considerations: The ethical approval was granted by hospital scientific committee. The study will adhere to ethical principles and guidelines to assure patient confidentiality.

Study Limitations: Because the study duration was shorter, the long-term effects of the therapy could not be assessed. It is possible that some data are missing due to inadequate documentation of the patient's medical records. All other adjuvant drugs may instigate and perpetuate the SEs due to the lack of conclusive evidence of causality and association related to drug administration and because the treatment is in a combination regimen.

Results

Among 34 pediatric cancer patients, 19 (55.9%) were females and 15 (44.1%) were males, with a male-to-female ratio of 1:1.27. The mean±sd (CI 95%) age of patients was 5.9±3.1 years, majority of them belonged to 5-8 years' interval (50%) as shown in figure 1.

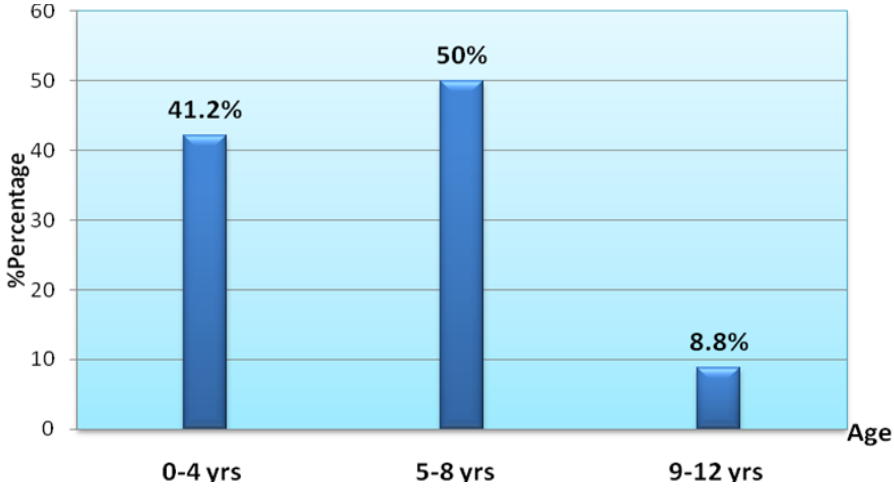

FIGURE (1). Distribution of pediatric leukemia patients according to age.

On analyzing type of pediatric leukemia 68% (n=23) of the patients were diagnosed with Acute Lymphoblastic Leukemia (ALL) and 32% (n=11) with Acute Myeloid Leukemia (AML) as illustrated in chart 2.

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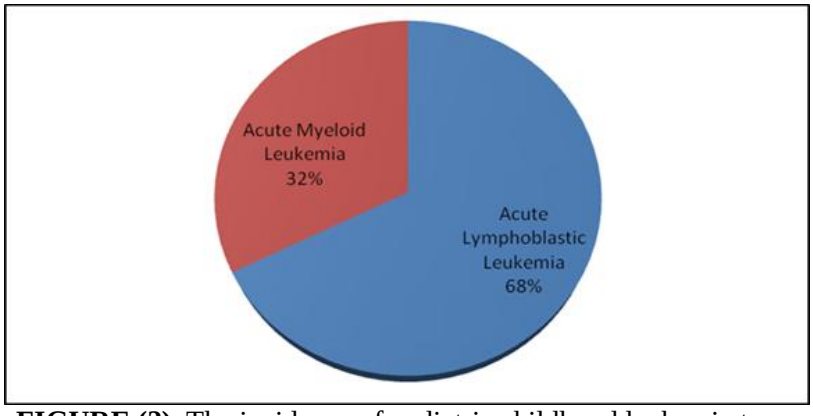

FIGURE (2). The incidence of pediatric childhood leukemia type.

Table (1) displays the drugs that are prescribed for pediatric cancer patients, the number of drug administrations in the study sample is represented by the frequency of prescription patterns. Vincristine was the most commonly used agent in pediatric leukemia patients, followed by L-asparaginase.

TABLE (1). Prescription patterns of chemotherapy drugs

no.	drug	drug class	prescription	Percentage (%)	95% ci for percentage
1	Vincristine	Vinca alkaloid	34	100%	100%-88.7%
2	L-asparaginase	Enzyme	27	79.4%	89.7%-63.2%
3	Methoteraxate	Antimetabolite	19	55.9%	71.1%-39.5%
4	Doxorubcin	Anthracycline	15	44.1%	60.5%-28.9%
5	Cytarabine	Antimetabolite	11	32.3%	49.2%-19.1%
6	PEG-asparginase	Enzyme	7	20.6%	36.8%-10.3%
7	Daunomycin	Anthracycline	5	14.7%	30.1%-6.4%
8	Cyclophosphamide	Alkylating agent	4	11.7%	23.1%-4.7%

In this study, 108 SEs due to cancer chemotherapy were reported in 34 patients (3.17 episodes per one patient). Neutropenia was the most commonly reported SEs followed by nausea & vomiting and fever, as summarized in table 2.

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TABLE (2). Patterns of chemotherapy-related side effects in pediatric leukemia patients.

no	side effects	frequency	percentage%	95% CI for percentage
1	Neutropenia	23	21.3%	30.0%-14.6%
2	Nausea &vomiting	13	12.0%	19.7%-7.0%
3	Thrombocytopenia	11	10.2%	17.5%-5.6%
4	Leukopenia	10	9.3%	16.4%-5.0%
5	Anemia	9	8.3%	15.3%-4.3%
6	Mucositis	9	8.3%	15.3%-4.3%
7	Infection	7	6.5%	13.0%-3.0%
8	Skin rash	7	6.5%	13.0%-3.0%
9	Constipation	7	6.5%	13.0%-3.0%
10	Electrolyte imbalance	5	4.6%	10.7%-1.7%
11	Diarrhea	4	3.7%	9.4%-1.1%
12	Peripheral neuropathy	3	2.8%	8.2%-0.6%
TOTAL N=		108	100%	

As shown in figure 3, the severity of reported SEs is graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 CTCAE (NCI.,2017). 48.1%% of reported SEs were severe, followed by 22.2% life-threatening.

TABLE (3). Common Terminology Criteria for Adverse Events CTCAE grades of reported chemotherapy-related side effects.

no	side effects	n	grade 1 mild	grade 2 moderate	grade 3 severe	grade 4 life-threatening
1	Neutropenia	23	2	5	10	6
2	Nausea &vomiting	13	1	3	6	3
3	Thrombocytopenia	11	1	3	6	1
4	Leukopenia	10	1	2	4	3
5	Anemia	9	1	2	4	2
6	Mucositis	9	1	1	5	2
7	Infection	7	1	1	3	2
8	Skin rash	7	1	1	3	2
9	Constipation	7	0	2	4	1
10	Electrolyte imbalance	5	1	1	2	1
11	Diarrhea	4	0	1	2	1
12	Peripheral neuropathy	3	0	0	3	0
TOTAL N=108		108	10	22	52	24
PERCENTAGE OF N %		100%	9.3%	20.4%	48.1%	22.2%

Discussion

In this study, it was observed that 19 (55.9%) patients were females and 15 (44.1%) were males, resulting in a male to female ratio of 1:1.27. The mean age of the patients was 5.9±3.1 years, with the majority (50%) falling within the 4-8 years' age interval. In a study

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by (Young et al., 1986) conducted in the United States, they reported a comparable male to female ratio of 1:1.25 among pediatric cancer patients. However, their study showed a slightly higher mean age of 6.3±2.8 years. The differences in age distribution might be attributed to racial factors specific to the American population. A study conducted by (Peris-Bonet et al., 2010) in Spain reported a wider age distribution, with the majority of patients falling within the 10-14 years' age interval. These discrepancies in age distribution might be influenced by variations in the inclusion criteria.

On analyzing pediatric leukemia cases, it was found that 68% of the patients were diagnosed with ALL, while 32% were diagnosed with AML. In a study by (Abushwereb et al., 2016), conducted in Libya, they reported an approximately similar prevalence of pediatric leukemia group with 74% of the patients diagnosed with ALL and 26% with AML. This consistency in results suggests similarities in disease distribution across different regions of the country. In contrast, a study by (Al-Hashimi,2021) in Iraq reported a lower incidence of ALL 33.3% and AML 12.9% among pediatric leukemia patients. The differences observed in leukemia group distribution between our study and theirs could be attributed to variations in study objectives, geographical locations, or the sample size of the respective studies.

Regarding the prescription patterns of anticancer drugs, our results indicate that vincristine was the most frequently used agent for pediatric leukemia patients, followed by L-asparaginase. These prescribing trends align with those reported in studies conducted in India (Manjesh et al., 2017). In our study cohort, consisting of 34 patients, a total of 108 SEs related to cancer chemotherapy were reported. This translates to an average of 3.17 episodes per patient. In contrast to our study (Kumar Behera et al., 2022), they reported a different finding: 1.18 SEs per patient. This could be attributed to the sampling difference, as our study only included pediatric leukemia patients. Neutropenia emerged as the most commonly reported SEs 21.3%, consistent with the findings of a study conducted in Egypt (Bader et al., 2016). Nausea and vomiting were reported in 12.0% of patients, closely mirroring the incidence rates reported in a study conducted in Kingdom of Saudi Arabia (Awwad et al., 2023), while thrombocytopenia was observed in 10.2% of patients. Although our study's results are in line with previous studies regarding the pattern of specific SEs. It is essential to

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acknowledge that there were variations exist between our study and previous studies conducted in different countries. These differences can be attributed to several factors, including variations in study design, data collection methods، drug prescribing practices, and dosing protocols. Additionally, variances in healthcare infrastructure, access to supportive care, and patients' adherence to treatment regimens may also contribute to differences in SEs.

Furthermore، our study revealed the severity of adverse drug reactions in pediatric leukemia patients based on the National Cancer Institute CTCAE، Version 5. The findings indicate that out of the total sample, 9.3% of patients experienced grade 1 SEs categorized as mild, while 20.4% exhibited grade 2 SEs considered moderate. Moreover, 48.1% of patients faced severe grade 3 SEs, while only 22.2% presented with life-threatening grade 4 reactions. When comparing these results with previous study conducted in Ethiopia, variations in the severity of chemotherapy-related SEs become evident. (Tola et al., 2023) reported a higher proportion of moderate Grade 2 reactions (42.7%), followed by (13.7.%) mild Grade 1 reactions and (10.3%) severe grade 3 reaction, and finally (1.07.%) life-threatening grade 4. The observed differences in the severity of SEs suggest the influence of several factors, including variations in the specific chemotherapy used, such as differences in drug formulations or availability and treatment protocols, lack of adherence to national and international guidelines in healthcare practices and access to supportive care, and the inadequacy of preventive measures and SEs monitoring.

Conclusions

Our study reveals the frequency and severity of chemotherapy-related side effects in pediatric leukemia patients and offers insights into chemotherapy drug prescription patterns. These findings underscore the importance of customized monitoring and interventions to address local factors influencing side effect outcomes. Further research is needed to develop preventive measures and optimize treatment plans for better patient outcomes.

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