Section: Pediatrics

Research

STUDY OF COMPLICATIONS DURING INDUCTION PHASE OF CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIC CHILDREN

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Abstract

Background: The most frequent cancer in children is acute lymphoblastic leukaemia (ALL). Chemotherapy is the best-suited treatment. However, complications are seen in each phase of chemotherapy, especially the induction phase. The focus of this research was to study the clinical signs and symptoms of problems in ALL children throughout the chemotherapy induction phase. **Materials and Methods:** The participants in this research were 45 recently diagnosed children with ALL who received induction chemotherapy for acute lymphoblastic leukaemia in our centre from January 2019 to July 2020. During the induction phase of chemotherapy, they were treated according to the Berlin-Frankfurt-Munster-95 protocol, in which 5 drugs were included. Data on demographics, clinical features, investigations, and management outcomes were collected from patient's case sheets and monitored daily in the haemato-oncology ward. **Result:** This study included 34 males and 11 females. Among study participants, 9.5% in the age group less than five years and 12.5% in age group five and above died. Fever was the common complication, followed by vomiting, hyperbilirubinemia, abdominal pain, mucositis, and tumour lysis syndrome. No significant association between gender and treatment outcome was found (p value=0.64 based on Fisher exact test). **Conclusion:** Fever was reported in 45 cases (100%), vomiting in 42 cases (93.3%), hyperbilirubinemia in 11 cases (24.4%), cushingoid characteristics in 8 cases (17.8%), and hypertension in 6 cases (17.8%). DIC was the least prevalent consequence with 5 (11.1%), bleeding symptoms with 5 (11.1%), infections with 5 (11.1%), death with 5 (11.1%), and febrile neutropenia with 4 (9%).

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a kind of leukaemia that affects lymphoid progenitor cells in the bone marrow, blood, and extramedullary tissues. The most frequent cancer in children is acute lymphoblastic leukaemia (ALL). It causes a quarter of all pediatric malignancies and around 75% of pediatric leukaemia cases.[1] According to Tyagi et al., the incidence of leukaemia in Indian children is 34%, with 25% of them having ALL[2] Between the ages of 2 and 5, the incidence of ALL occurrence is highest.[3,4,5]

ALL is a blood malignancy with chromosomal abnormalities which originates from either the T-cell or B-cell lineages.[6,7,8]

There is a small male predominance in ALL. The probability of the second twin developing ALL is higher than in the general population if one twin has ALL. Children with Down syndrome, Poland syndrome, Fanconi anaemia, Bloom syndrome, and other genetic and immunodeficiency disorders are more prone to develop ALL than the general population.[4]

Chemotherapy is the most common mode of cancer treatment. Chemotherapy can be used to cure a disease or prolong life or relieve symptoms. Anticancer drugs either kill cancer cells or impact their growth factors. They might inhibit specialized signaling pathways, angiogenesis, tumor antigens, and other factors that are involved in the cell cycle's various phases. This process unfortunately may also disturb the cell cycles of non-cancerous actively proliferating cells, resulting in a range of problems.

The majority of contemporary paediatric protocols are designed on the basis that was created by Dr Riehm for the BFM research group (Berlin Frankfurt-Munster). The process of therapy entails

- induction/consolidation,
- interim maintenance,
- reinduction/reconsolidation (often referred as delayed intensification), and

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• maintenance phases.

Vincristine (VCR), l-asparaginase (l-ASP), corticosteroids (PDN), and daunorubicin (DNR) are used in a four-drug induction, followed by cyclophosphamide (CPM), cytosine arabinoside (ARA-C), and 6-mercaptopurine (6-MP) consolidation, and intense intrathecal methotrexate (MTX) with or without cranial irradiation.[7]

The present study has considered the complications arising during the induction phase only. Since of the immunosuppressive nature of the illness and the chemotherapy regimen utilised, the induction phase was chosen to evaluate the non-infectious and infectious complications profile because this is the phase during which the risks of problems are highest. Knowing complications during the induction phase of chemotherapy in ALL children helps us to anticipate and manage problems arising during chemotherapy and formulate a better treatment regimen to improve the quality of life during anticancer treatment.

MATERIALS AND METHODS

This observational study was conducted in the Haemato-oncology ward, Institute of Child Health and Research Centre, Government Rajaji Hospital & Madurai Medical College between January 2019 and July 2020. The institutional ethics committee provided ethical approval. A total of 45 children took part in the study.

Inclusion Criteria

Children admitted with acute lymphoblastic leukaemia were included in this study.

Exclusion Criteria

Children presenting with haematological malignancies other than ALL were excluded.

After a thorough description of the method, the participants gave their informed verbal and written consent.

A detailed social and medical history was taken from each patient, including name, age, sex, clinical profile, investigations, and treatment details.

Participants of the study were treated according to BFM (Berlin-Frankfurt-Munster)-95 protocol.

This protocol includes following drugs in induction phase of chemotherapy:

1. Tablet prednisolone (60mg /m2 /day)
2. Injection Vincristine (1.5mg/m2 /dose)
3. Injection Daunorubicin (30mg/m2 /dose)
4. Injection L-asparaginase (5000 IU/m2 /dose)
5. Intrathecal Methotrexate (12mg/dose).

Complications were reported and recorded systematically. All the data was collected methodically and analyzed.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 21.0 was used for all analysis of the data. The percentage of children who experienced problems during the induction phase of chemotherapy was calculated. The statistical significance of the data was determined using the chi-square test and Fisher exact test. At p-0.05, statistical significance was evaluated.

RESULTS

According to Table 1, 21(46.7%) children were between 0-5years, 18(40.0%) were between 5-10years, whereas 6 (13.3%) were more than 10 years of age. Among 45 participants, 34(75.6%) were male, while 11(24.4%) were female, as seen in [Table 1] The percentage of distribution of presenting symptoms was 7(15.6%) Fever, 12(26.7%) Abdominal pain, neck swelling 9(20%), joint pain 9(20%) and 7(15.6%) headache. 88.9% of the cases presented with B -Cell Leukemia, while the rest (11.1%) had T -Cell Leukemia.

[Table 2] shows the distribution of infectious and non-infectious complications during the induction phase of chemotherapy in pediatric ALL patients. All (100%) patients presented with fever. The next most common complication was vomiting.

[Table 3] shows post-chemotherapy complications. Steroid-related toxicity caused cushingoid features in 8 children, while hypertension was reported in 6. 40 children had epistaxis and gum bleeding. Liver parameters showed increased bilirubin levels in 38 participants.

The microbiological profile showed no growth in 30 children, while klebsiella growth was found in 3 children (6.7%), and pseudomonas growth was seen in 2 children [Table 4].

Ultrasonography showed mild hepatomegaly in 7(15.6%) children, while moderate hepatomegaly was seen in 3 (6.7%) children [Table 4].

Among 45 ALL children, recovery was seen in 40(88.9%) cases, while death was seen in 5(11.1%) during the induction phase of chemotherapy [Table 4].

Table 1: Patient characteristics distribution

Patient characteristics		Frequency	Percentage
Age group	0 to 5	21	46.7%
	5 to 10	18	40.0%
	>10	6	13.3%
Gender	Male	34	75.6%
	Female	11	24.4%
Symptoms	Fever	7	15.6%
	Abdominal pain	12	26.7%
	Neck swelling	9	20.0%

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	Joint pain	9	20.0%
	Headache	7	15.6%
Type of leukaemia	B cell leukaemia	40	88.9%
	T cell leukaemia	5	11.1%

Table 2: Non-infectious and infectious complications among study participants

Complication	Frequency	Percentage
Fever	45	100.0%
Vomiting	42	93.3%
Hyperbilirubinemia	11	24.4%
Mucositis	5	11.1%
Tumour lysis syndrome	1	2.2%
Cushingoid features	8	17.8%
Gum bleeding	3	6.7%
Thrombophlebitis	3	6.7%
Epistaxis	2	4.4%
Hypertension	6	13.3%

Table 3: Post Chemo Complications

Patient characteristics		Frequency	Percentage
Steroid Toxicity	Hypertension	6	13.3%
	Cushingoid features	8	17.8%
	No signs	31	68.9%
Gum bleeding and epistaxis		40	88.9%
Liver Parameters	Increased total bilirubin	38	84.4%
	Elevated SGOT	13	28.9%
	Elevated SGPT	4	8.9%
	Elevated ALP	7	15.6%

Table 4: Distribution of outcome

Patient characteristics		Frequency	Percentage
Microbiological profile	Pseudomonas growth	2	4.4%
	Klebsiella growth	3	6.7%
	No growth	40	88.9%
USG abdomen findings	Normal	35	77.8%
	Moderate hepatomegaly	3	6.7%
	Mild hepatomegaly	7	15.6%
Outcome	Recovered	40	88.9%
	Death	5	11.1%

DISCUSSION

This observational study was conducted to determine the occurrence of non-infectious and infectious complications in children with ALL during induction chemotherapy.

The age at which a child is diagnosed has been identified as a significant predictive factor for the incidence and survival of paediatric ALL[9]. According to several researchers, all patients identified between the ages of 1 and 9 have the highest probability of survival.[10,11,12] In our study, 46.7% of the ALL cases were seen in 5 years and below children. Therefore, the recovery rate was higher in this study.

To account for the useful analysis of age at diagnosis, several researches have attempted to identify particular genetic and biochemical processes that occur in different age groups. For instance, cytogenetic markers such as the chromosomal rearrangement TEL/AML1 and DNA index ≥ 1.16, which peak at newborn and preschool age, are linked to a better chance of survival. In contrast, The BCR/ABL rearrangement, which is much lower in individuals aged 1–4 years, is linked to poor survival.[13]

This study depicts that paediatric ALL has a higher male prevalence. Similar findings were obtained by Khalid et al,[14] in a retrospective study.

In our study, among 45 ALL children, fever was a non-infectious complication seen in all 45(100%) study participants. However, compared to the previous study conducted by Rajeswari et al,[15] and Hassan et al,[16] fever was seen in 42(28%) patients and 22 (36%) patients respectively.

Chemotherapy-induced nausea and vomiting (CINV) is a severe cancer treatment side effect that affects up to 40% of patients.[17] In our study, vomiting as a complication was seen in 42(93.3%) out of 45 study participants. Compared to the previous study conducted by Hassan et al,[16] vomiting was seen in 42(70%) patients out of 52 cases. Patient gender (females >males), age (>3 years), history of CINV, the medicine's emetogenic potential, and chemotherapy delivery schedule are all risk factors for CINV. Several pathways exist for chemotherapeutic medicines to cause nausea and vomiting. They induce vomiting by disturbing the mucosal lining of the stomach and duodenum, The vomiting centre (VC) and the chemoreceptor trigger zone in the brain are both activated by this (CTZ). They can also stimulate the CTZ by obstructing the

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intestines, delaying gastric emptying, or producing inflammation. As a result, CINV involves the interaction of multiple organs of the gastrointestinal tract, as well as the peripheral and central neurological systems.[18,19]

In the present study, hyperbilirubinemia was seen in 11 (24.4%) out of 45 cases. According to a study by Denton et al,[20] During Induction, 4.9% of patients experienced hyperbilirubinemia (conjugated and unconjugated).[21] Miron et al,[22] reported hyperbilirubinemia in 61% of cases. Hepatomegaly and moderate liver dysfunction are common symptoms in children with acute lymphoblastic leukaemia (ALL). A rare consequence of leukaemia is severe jaundice. Jaundice can result from drug-induced liver injury, viral infections, tumour cell infiltrations, and hemolysis.[21]

Among the 45 participants of this study, mucositis was seen in 5(11.1%). Erythema, ulcerations, oedema, and bleeding are all symptoms of mucositis. This disorder affects the ventral region of the tongue, the floor of the mouth, and the soft palate in the oral mucosa.[23] Oral mucositis is the most frequent and debilitating stomatological complication in chemotherapy patients for leukaemia and other cancers. The anti-cancer drugs vincristine and daunorubicin are toxic to the mucosa.[24] The use of these medications or cancer causes neutropenia, which makes the mucosa more susceptible to mucositis lesions and allows bacteria to invade the submucosa and vascular walls, resulting in bacteremia and septicaemia.[25] Azher et al. reported that OM is diagnosed in 20% of ALL patients undergoing induction chemotherapy, and 25% of patients getting induction treatment with radiation.[26]

Tumour lysis syndrome is seen in 1(2.2%), and compared to the study conducted by Bagshi et al,[27] Tumor lysis syndrome is seen in 19% of cases. The tumour lysis syndrome occurs when tumour cells spontaneously or in reaction to therapy discharge their contents into the bloodstream, resulting in hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. In addition, renal insufficiency, cardiac arrhythmias, seizures, and death due to multiorgan failure are possible outcomes of these electrolyte and metabolic abnormalities.[28]

Cushingoid features were recorded in 8(17.8%) cases in this study, while in a previous study conducted by Miron et al,[22] Cushingoid features were seen in 21.5% of cases. According to a study published by Danon et al, on the correlation between Cushing's syndrome and leukaemia, it was found that the hypothalamus and limbic system had the most leukemic infiltrates in brain tissue. Therefore, basophilic hyperplasia, ACTH hypersecretion, adrenocortical hypertrophy, and clinical Cushing's syndrome are thought to have resulted from the damaging leukemic infiltration of the limbic system, which eliminated a moderating impact on pituitary function.[29,30,31,32,33,34,35]

Bleeding manifestations were seen in 5(11.1%) participants. On the contrary, bleeding manifestations were reported in 100% of cases in a study by Miron et al,[22] Chemotherapy-induced hematopoiesis suppression is a typical side effect, resulting in cancer treatment delays or dose reductions. Although there are a variety of causes for chemotherapy delays or dose reductions, marrow suppression is one of the most common.[29]

According to our study, 6 patients developed hypertension. Glucocorticoids are frequently used during induction treatment and as pulse therapy throughout maintenance has been one of the reasons leading to better cure rates in paediatric ALL. Glucocorticoids are shown to cause HTN in several studies. The overstimulation of the mineralocorticoid receptor is the primary mechanism of corticosteroid-induced HTN. This causes sodium retention in the kidneys, which leads to volume expansion and a rise in blood pressure.[30]

Out of 45 children with ALL, 5(11.1%) cases developed DIC in our study. According to a study by Songthawee 31, out of 81 children with ALL receiving chemotherapy, 12 reported (14.8%) with DIC while 69 (85.2%) without DIC. DIC is characterised by spontaneous or induced bleeding problems, as well as thrombotic issues, Multiple organ failures can occur as a result of intravascular fibrin development. Additionally, the generation of several proteolytically active clotting cascade enzymes may increase inflammatory activity, worsening the systemic inflammatory condition.[32]

Only 4 cases of neutropenia were reported in this study. Chemotherapy-induced neutropenia is a frequent side effect of cancer treatment and one of the most important dose-limiting side effects in clinical trials. In a prospective cohort study, out of 50 pediatric patients receiving chemotherapy, Only 28% of patients experienced substantial neutropenia for the first time, while 72% had recurring episodes during therapy.[33] In addition, research shows that Early-onset neutropenia has been linked to induction blocks used to treat ALL and AML (3.66±1.5 vs 5.4±2.1 days, respectively) compared to the late onset of neutropenia in individuals on ALL maintenance treatment.[34]

CONCLUSION

Our study highlights the most common complications in ALL children during the induction phase of chemotherapy. Reported complications were fever in 45(100%), vomiting in 42(93.3%), hyperbilirubinemia in 11(24.4%), cushingoid features in 8(17.8%) and hypertension in 6(13.3%). The least common complications were DIC in 5 (11.1%), bleeding manifestations in 5(11.1%), %), infections in 5 (11.1%), death in 5 (11.1%) and febrile neutropenia in 4(8.9%). Because of their immunosuppressive status caused by the disease and chemotherapy, children with ALL were more

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susceptible to infective and non-infectious complications.

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