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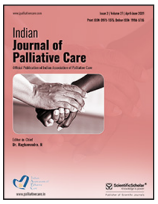

Original Article

Evaluation of Chemotherapy Induced Peripheral Neuropathy, Sarcopenia and Fatigue in Children with Acute Lymphoblastic Leukaemia and Lymphoma in Tertiary Care Hospital, Dakshina Kannada

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ABSTRACT

Objectives: The study aims to assess the proportion and magnitude of chemotherapy-induced peripheral neuropathy (CIPN) and other common complications reported in children with acute lymphoblastic leukaemia (ALL)/ acute lymphoblastic lymphoma (LBL) undergoing chemotherapy.

Material and Methods: The study included children between 5 and 18 years old with ALL/LBL undergoing chemotherapy in Tertiary Care Hospitals, Mangalore. The study was conducted using various instruments, including paediatric-modified total neuropathy scale for CIPN, handheld dynamometer for muscle strength, bioimpedance analyser for muscle mass, timed up-and-go test for physical performance, and national comprehensive cancer network (NCCN) guidelines for scoring cancer-related fatigue at 3-time points. The collected data were analysed by IBM Statistical Package for the Social Sciences version 29 using Z-scores with standard deviation for distinct ALL/LBL types. In addition, the Paired *t*-test compared the baseline outcome to the 3rd and 6th time points.

Results: The study evaluated 25 children with ALL undergoing chemotherapy based on the UKALL 2003 protocol during their maintenance phase. The study found that 25 children experienced CIPN, with changes in sensory and pin sensibility scores at 3 and 6 months. The study found a significant change in handgrip strength, body mass index, and muscle mass at 3 months, with no significant change in physical performance over time. Fatigue scores increased from baseline to 3 months, with significant changes observed for the 7–12 years age group at 3 months but not for the 5–6 years age group at 6 months.

Conclusion: Children with ALL/LBL undergoing chemotherapy experience CIPN and other side effects such as sarcopenia and fatigue. The study highlights the potential benefits of physiotherapy interventions and supportive care strategies aimed at managing the adverse effects of chemotherapy in children with ALL/LBL.

Keywords: Chemotherapy-induced peripheral neuropathy, Sarcopenia, Fatigue, Acute lymphoblastic leukaemia, and lymphoma

INTRODUCTION

Haematological or blood cancers, including leukaemia and lymphoma, affect the immune system or blood-forming tissues. Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer and arises from the unregulated growth of clonal lymphoid cells. Acute lymphoblastic lymphoma (LBL) is a rare and highly aggressive neoplasm of lymphoblast, which shares features with ALL but is distinguished by less frequent central nervous system involvement and extension of bone marrow involvement.[1-5]

Childhood cancer is a significant global health challenge, with over 280,000 children and adolescents diagnosed with cancer in 2020, resulting in almost 110,000 deaths worldwide. Diagnosis is challenging in many countries, so the actual number of cases may be higher. Over 80% of children with cancer survive in high-income countries, but more data are needed in India.

Leukaemia is more prevalent in the Indian population, especially in the age group of 6–10.[6-8]

Treatment for ALL/LBL includes surgery, radiation, chemotherapy, targeted drug therapy, immunotherapy,

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and stem-cell transplant. The specific approach depends on factors such as cancer type, stage, and child's age. Three regimens (A, B, and C) determine treatment intensity and duration varies across phases. There are five phases of chemotherapy. The induction phase involves intensive chemotherapy to eliminate leukemic cells from the body, requiring hospital stays. The consolidation phase focuses on removing leukemic cells from the blood and bone marrow, preventing them from expanding to the brain and spinal cord. The interim maintenance phase is less intensive and is mainly given orally. The delayed intensification phase aims to clear the remaining leukemic cells, primarily done on an outpatient basis. The maintenance phase is mostly outpatient and lasts for 2–3 years. Recovery may vary, and it may take some time for children to return to their routine life.[3,9-13]

Chemotherapy drugs used in childhood cancer treatment, such as vinca alkaloids and platinum compounds, commonly cause chemotherapy-induced peripheral neuropathy (CIPN). Vincristine (VCR) can lead to symptoms such as muscle weakness, paraesthesia, and dysesthesia, affecting up to 90% of children, depending on the dose.[9,10] Childhood cancer survivors face the risk of sarcopenia, characterized by muscle loss, which can impact physical function and quality of life. Assessing skeletal muscle health is crucial for evaluating metabolic disease risk and falls.[14,15] Cancer-related fatigue (CRF) is persistent tiredness or exhaustion that hampers daily activities. CRF may be caused by neurotoxic drugs, metabolite accumulation, malignancy, or low blood count, but limited evidence supports these theories.

Understanding the side effects of treatment is essential in children, as children may function normally but suffer deterioration compared to healthy children. This study evaluates these conditions at three different time points in the Indian population, which can help manage persistent treatment-related side effects to ensure that children can return to their routine lives. However, despite increasing evidence regarding the prevalence of these conditions, limited research has been conducted on them during the maintenance phase in children with ALL/LBL. Even though some studies suggest their presence, more studies are needed to examine outcome measures for these conditions in this patient population.

MATERIAL AND METHODS

A longitudinal study was conducted from February 2022 to January 2023, using convenience sampling in tertiary care hospitals on a daycare basis. The study included children aged 5–18 undergoing chemotherapy for ALL and lymphoma receiving chemotherapy protocol UKALL 2003 in their maintenance phase. The required Eastern Cooperative Oncology Group performance status scale score was ≤2 for inclusion in the study. The study excluded children with severe orthopaedic or neurological dysfunctions and those with metastasis that could limit their participation. The study obtained approval from the institutional ethics committee and written informed consent and assent forms from parents and children above 7 years old, respectively.

Study participants who fulfilled the eligibility criteria were evaluated at 3-time points, that is, at baseline in the maintenance phase, 3 and 6 months. Children were assessed for CIPN using the paediatric modified total neuropathy scale (Ped-mTNS), Sarcopenia was assessed for handgrip strength using the JAMAR handgrip dynamometer, muscle mass using bioimpedance analyser (BIA) [OMRON HBF 225T] and physical performance by timed up-and-go (TUG) test. Fatigue was assessed using NCCN fatigue guidelines.

CIPN in school-aged children was assessed using the Ped-mTNS scale, which included a questionnaire and clinical testing. The questionnaire covered sensory, functional, and autonomic sensations, whereas the clinical testing involved light touch, pin sensibility, vibration, manual muscle testing (MMT), and deep tendon reflex (DTR). Each part was scored from 0 to 4, resulting in 32 scores. The severity of the condition increased with higher scores. Light touch sensation was tested using a Semmes–Weinstein monofilament, pin sensibility with a paper pin, vibration sensation with a biothesiometer, and DTR using a knee hammer at the knee and Achilles tendon.

Sarcopenia muscle mass was evaluated using a BIA. Children's height, age, and gender were entered into the device, and muscle mass was recorded. Handgrip strength was measured using a handheld dynamometer. Children sat on a chair with their arms adducted, elbows flexed to 90°, and forearms in a neutral position. The test was conducted 3 times with 1-min rest intervals, and the highest reading in kilogram-force was recorded. Physical performance in the paediatric population was assessed using a chair and measuring the height concerning 90° of knee flexion. Children were asked to sit relaxed and then stand up and walk 3 m, measured with an inch tape, before sitting back down. Instructions to walk fast were not given and children were allowed to act naturally.

Fatigue was measured using NCCN guidelines, where we asked the children to rate the fatigue over the past 7 days. According to NCCN guidelines, for children >12 years, fatigue was scaled from 0 to 10 where 0 – no fatigue and 10 is the worst fatigue, 1–3 indicates mild, 4–6 indicates moderate and 7–10 indicates severe fatigue. For children 7–12 years, 1 – no fatigue, 2 – mild fatigue, 3 – moderate fatigue, 4 – severe fatigue and 5 – worst fatigue. Children 5–6 years old were asked if they felt tired or not.

The data collected were entered into the IBM Statistical Package for the Social Sciences version 29 SPSS. $P < 0.05$ was considered statistically significant. Z-scores with standard deviation for the participants for each outcome variable were calculated for different types of ALL/LBL. A paired *t*-test was performed for each outcome variable to compare the 3rd and

6th time points from the baseline. All tests used one side of statistical significance.

RESULTS

Among 25 participants included in the study, 28% were from the 5–6 years of age group, followed by 52% in the 7–12 years and 60% of participants were male. Of the participants, 76% had B-cell leukaemia, 16% had T-cell leukaemia and 8% had lymphoma. About 40% of participants were there in each A and C regimen. The post-chemotherapy duration was 16% in <6 months, 40% in 6–12 months, and 44% in 12–24 months [Table 1].

[Table 2] shows the comparison of CIPN scores for all study participants; functional, autonomic, light touch, MMT, and total CIPN scores had changes in scores over 3 and 6 months, with significant changes in functional ($P = 0.030$) and total CIPN score ($P = 0.015$) at 6 months. Sensory and pin sensibility score values decreased at 3 months from baseline but increased at 6 months, with a significant change in pin sensibility at 3 months ($P = 0.004$) and at 6 months ($P = 0.041$). There was a considerable change ($P = 0.001$) in DTR scores (worsening) from baseline to 6 months.

[Table 3] compares sarcopenia scores for all study participants, where the handgrip strength significantly increased from baseline to 3 months ($P = 0.003$) and baseline to 6 months ($P = 0.002$). The body mass index (BMI) and muscle mass did not significantly change at 6 months from baseline but showed a significant increase ($P = 0.020$ and $P = 0.037$, respectively) at 3 months from baseline. The body fat percentage and physical performance showed no significant change from baseline to 3 months for both the components, whereas physical performance did not change values at 6 months.

The mean fatigue scores increased from baseline to 3 months for both the 5–6 years and >12 years of age groups, and there was a further increase in mean scores for the 5–6 years of age group at 6 months. Despite the increase in mean scores, there was no significant change in the *P*-value said to be 0.091 for the 5–6 years of age group at 6 months. For 7–12 years, there was a significant change ($P = 0.019$) at 3 months, but scores were higher at 6 months than at baseline [Table 4].

Table 1: Characteristics of all study participants.

Characteristics	Overall (*n*=25)	
	Frequency	Percentage
Age group (in years)		
5–6 years	7	28
7–12 years	13	52
>12 years	5	20
Gender		
Male	15	60
Female	10	40
Diagnosis		
B-cell leukaemia	19	76
T-cell leukaemia	4	16
Lymphoma	2	8
Regimen^		
A	10	40
B	5	20
C	10	40
Post-chemotherapy duration (in months)		
<6 months	4	16
6–12 months	10	40
12–24 months	11	44

^Regimen. A: Three-drug induction phase, B: Four-drug induction phase, C: Four-drug induction, augmented BFM consolidation, Capizzi interim maintenance and two further BFM-style intensification periods of extended duration

DISCUSSION

The present study provides valuable insights into CIPN, sarcopenia, and fatigue as common side effects of chemotherapy in children with ALL/LBL. The study evaluated these side effects longitudinally over a 6 month follow-up period.

Regarding CIPN, the present study employed a comprehensive approach, including subjective and clinical assessments. The results indicated that functional, autonomic, light touch, MMT, and total CIPN scores significantly improved at 3 and 6 months compared to baseline evaluation. This improvement is likely attributed to reduced and spaced-out doses of VCR administered during the maintenance phase of chemotherapy. However, sensory and pin sensibility scores initially improved at 3 months but deteriorated again at 6 months, with a significant change in pin sensibility. This fluctuation could be linked to the analgesic medication gabapentin/gabaneuron (200 mg/m^2), which showed temporary symptom improvement during chemotherapy. Despite medication use, DTR scores consistently remained worse at all 3-time points, suggesting that VCR continued to impact DTR with no effect of analgesia. Vincristine-induced peripheral neuropathy (VIPN) scores have been shown in the literature to be worse in older children. While most children experienced only mild-to-moderate VIPN, others developed severe symptoms.[16] Reducing the amount of vincristine given or spreading out the dosing schedule can help alleviate peripheral neuropathic pain caused by vincristine.[17,18] The article discusses the symptoms and diagnosis of CIPN, which can be subjective and challenging to diagnose. A study found that gabapentin effectively alleviated pain in adult patients with painful CIPN.[17,19] However, another study found no difference in symptom severity between patients who received gabapentin and placebo.[17,20] It is recommended to adjust the dose and add other medications to enhance the efficacy of gabapentin in treating CIPN. The use of analgesic medications was not quantified, which may have impacted pain assessments in patients.[17]

Table 2: Comparison of CIPN scores for all study participants.

Outcome	Baseline (B) (*n*=25) Mean z score±SD	3-month (TM) (*n*=22) Mean z score±SD	6-month (SM) (*n*=14) Mean z score±SD	P (B vs. TM) (*n*=22)	P (B vs. SM) (*n*=14)
Sensory	1.32 (1.43)	1.18 (1.29)	1.29 (1.32)	0.439	0.274
Functional	1.04 (1.45)	0.86 (1.12)	0.36 (0.49)	0.183	0.030*
Autonomic	1.00 (1.44)	0.95 (1.17)	0.93 (0.91)	0.314	0.315
Light touch	1.92 (0.99)	1.86 (1.03)	1.79 (1.05)	0.317	0.075
Pin sensibility	1.40 (1.47)	0.86 (1.52)	1.21 (1.47)	0.004*	0.041*
Vibration	2.24 (1.09)	2.32 (1.04)	2.21 (1.18)	0.226	0.336
MMT	1.12 (0.88)	0.82 (0.85)	0.64 (0.74)	0.016*	0.016*
DTR	0.92 (0.90)	1.18 (1.09)	2.00 (1.17)	0.118	0.001*
Total CIPN score	10.96 (4.14)	10.09 (3.50)	9.43 (2.92)	0.085	0.015*

**P<0.05.* SD: Standard deviation, CIPN: Chemotherapy-induced peripheral neuropathy, DTR: Deep tendon reflex, MMT: Manual muscle testing

Table 3: Comparison of sarcopenia scores for all study participants.

Outcome	Baseline (B) (*n*=25) Mean z score±SD	3-month (TM) (*n*=22) Mean z score±SD	6-month (SM) (*n*=14) Mean z score±SD	P (B vs. TM) (*n*=22)	P (B vs. SM) (*n*=14)
Handgrip strength (kg)	7.20 (6.01)	9.23 (7.45)	11.29 (8.25)	0.003*	0.002*
BMI (kg/m^2)	15.66 (2.79)	16.18 (3.02)	16.9 (4.03)	0.020*	0.091
Muscle mass$^+$ (%)	23.92 (6.74)	25.21 (7.51)	25.50 (8.85)	0.037*	0.184
Body fat^{++} (%)	17.76 (7.18)	17.43 (9.80)	18.52 (10.75)	0.213	-
Physical performance (seconds)	8.27 (2.72)	8.80 (2.47)	8.29 (2.01)	0.206	0.421

$^+$Muscle mass (*n*) – baseline (19), 3 months (19), 6 months (13), B versus TM (17), B versus SM (11), $^{++}$Fat% (*n*) – baseline (6), 3 months (18), 6 months (12), B versus TM (4), B versus SM (0), **P*<0.05, SD: Standard deviation, BMI: Body mass index

Table 4: Comparison of fatigue scores for all participants.

Outcome	Baseline (B) (*n*=25) Mean z score±SD	3-month (TM) (*n*=22) Mean z score±SD	6-month (SM) (*n*=14) Mean z score±SD	P (B vs. TM) (*n*=22)	P (B vs. SM) (*n*=14)
5–6 years	0.20 (0.44)	0.40 (0.54)	0.75 (0.50)	0.187	0.091
7–12 years	1.58 (0.51)	1.25 (0.45)	1.67 (0.81)	0.019*	0.305
>12 years	2.80 (2.04)	3.80 (3.63)	1.25 (1.50)	0.334	0.160

**P*<0.05, SD: Standard deviation

This information can guide the development of physiotherapy interventions that target specific CIPN symptoms that tend to worsen over time, such as autonomic symptoms and DTR scores. In addition, the findings on sensory and pin sensibility score values improving at 3 months but decreasing at 6 months can inform the timing and duration of physiotherapy interventions to address these symptoms. Even though some children received gabapentin, the CIPN can still cause significant sensory impairments (pin sensibility and light touch) in cancer patients.

The current study also observed improved handgrip strength from baseline to 3 and 6 months, but there was no significant improvement in BMI and muscle mass after 6 months. In addition, there was no significant change in body fat percentage or physical performance from baseline to 3 or 6 months. Our study is consistent with Akyay *et al*. 2014, where handgrip strength improved to a normal level over time, but TUG duration remained lower than normal even after a mean of 13.8 months. The results suggest that while muscle strength and function may improve over time after ALL treatments, the muscles of the lower extremities may be more affected than those of the upper extremities.[5] The improvement in BMI and muscle mass observed in our study was attributed to regular nutritional intake and everyday physical activity. Our participants were educated regarding the positive benefits of physical activity and nutrition on BMI and muscle mass. This finding was conversely proven by Rayar *et al*. (2012). They reported that the lack of nutritional intervention and decreased physical activity reduced muscle mass in the study population. These findings suggest that

proper nutrition and regular physical activity are essential for maintaining muscle health in ALL patients.[21]

The present study assessed cancer related fatigue in pediatric patients receiving maintenance therapy for ALL and lymphoma utilising age-specific scoring methods recommended by NCCN guidelines. The study indicates an increase in mean fatigue scores over time for both the 5–6 years and >12 years age groups. Furthermore, the 5–6 years age group experienced a further increase in scores at 6 months, while there was a significant change in scores for the 7–12 years age group at 3 months, but the scores were higher at 6 months than baseline. This finding suggests that fatigue is prevalent across different age groups and may require ongoing attention and intervention. Studies conducted earlier have shown that children with ALL suffer from disrupted sleep–wake cycles, reduced physical activity, and higher levels of fatigue related to cancer, especially when they take dexamethasone, compared to healthy children. A relationship between sleep–wake rhythm disturbances and cancer-related fatigue has been previously described in paediatric oncology populations, suggesting that sleep patterns may play a role in developing cancer-related fatigue.[22]

There were eight children lost follow-up from 3 to 6 months, attributed to non-compliance with scheduled follow-up visits. This non-compliance was primarily due to prioritising school exams and operational difficulties, such as their limited availability on a daycare basis and the need to adhere to fixed departure times for long-distance travel.

This study has three main limitations. The first is the small sample size and wide age range of children, which cannot generalise the result. The second is that the study was limited to two hospitals in Mangalore. Finally, our study primarily focuses on immediate chemotherapy complications over a 6-month follow-up period thus long-term effects are not assessed.

CONCLUSION

In our study, all children during the maintenance phase of chemotherapy experienced CIPN symptoms such as sensory and pin sensibility, which showed transient improvement probably due to analgesic administration, with worsening of the values post-withdrawal of the analgesia. DTR, however, continued to worsen over time. Our study further demonstrated that handgrip strength improved over time, with no change in physical performance. Fatigue scores suggest younger children are more prone to fatigue than older children. The findings of this study may contribute to the development of physiotherapy interventions and other supportive care strategies aimed at early rehabilitative management of adverse effects of chemotherapy in children with ALL/LBL.

Ethical approval

The author(s) declare that they have taken the ethical approval from IRB/IEC.

Declaration of patient consent

Patient's consent was not required as patients identity was not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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