Effect of Smart Pill Box on Improving Adherence to 6-Mercaptopurine Maintenance Therapy in Pediatric ALL

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Abstract

Introduction 6-Mercaptopurine (6-MP) forms the backbone of maintenance chemotherapy for acute lymphoblastic leukemia (ALL). A Children's Oncology Group study found 3.9-fold increased risk of relapse in children with 6-MP adherence less than 90%.

Objective This article estimates the impact of smart pill box in improving adherence to 6-MP during maintenance phase chemotherapy in children with ALL.

Materials and Methods It is a prospective interventional study done at pediatric oncology clinic of a tertiary care hospital. Participants being 40 newly diagnosed children with ALL. Baseline adherence was assessed and impact of smart pill box was estimated after using it for 60 days. Subjective and objective assessment of baseline adherence and adherence after intervention was done by subjecting the parents of the children to Morisky Medication Adherence Score 8 (MMAS-8) and measurement of patient's red blood cells (RBC) 6-MP metabolites (6-thioguanine [TGN] and 6-methylmercaptopurine [MMP]) levels, respectively, pre- and postintervention.

Results The mean age was 7.39 ± 4.29 years. NUDT15*3 polymorphism was present in 10.26%, and none had *TPMT* polymorphism. Baseline assessment of adherence to 6-MP by MMAS-8 revealed low, medium, and high adherence in 7.5, 35, and 57.5%, respectively. Baseline 6-TGN and 6-MMP levels by cluster analysis revealed poor adherence in 10%. Following intervention, mean MMAS-8 improved from 7.34 ± 0.78 to 7.66 ± 0.55 (p-value < 0.015) and the median 6-TGN level improved from 150 to 253 pmol/8×10^8 RBCs (p-value < 0.001).

Conclusion Nonadherence to 6-MP is widely prevalent in Indian children. Simple measures like smart pill box can improve adherence.

Keywords
- ALL
- maintenance chemotherapy
- adherence
- smart pill box
- 6MP metabolites

Introduction

Acute lymphoblastic leukemia (ALL) is among the most common malignancies in children. Cure rates vary between the risk groups and in developed countries cure rates are up to 90% in low-risk group.[1–4] Maintenance chemotherapy of 2 to 2.5 years of duration is an essential component of the treatment to achieve long-term disease-free remission in ALL.[5–7] Daily oral 6-mercaptopurine (6-MP) and weekly methotrexate administration form the backbone of

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maintenance chemotherapy.[6] Similar to other conditions requiring chronic oral intake of medications, nonadherence to 6-MP is frequently reported in children with ALL.[8,9] Moreover, children are asymptomatic during maintenance phase which may further increase chances of nonadherence. Nonadherence to 6-MP puts them at increased risk of relapse. Indeed, a Children's Oncology Group (COG) study by Bhatia et.al found 3.9-fold increased risk of relapse in children with less than 90% adherence.[8] This increased relapse risk has greater significance in the context of resource-limited setting as observed in most low-and-middle income countries (LMICs), as children with relapsed ALL have very poor access to intensive and novel therapy required for the cure.[10] Lack of adherence to 6-MP has been studied in children with ALL from developed countries.[9] Yet, little is known about its prevalence in LMICs.

Adherence to 6-MP can be measured by various methods including pill count, smart monitoring system, parent and/or child self-report, or therapeutic drug monitoring.[11] 6-MP has short half-life of 1.5 hours.[8] Hence, 6-MP level is not useful for therapeutic monitoring. However, 6-MP metabolites 6-thioguanine (6-TGN) and 6-methylmercaptopurine (6-MMP) accumulate in red blood cells (RBCs) over 1 to 3 weeks and monitoring 6-MP metabolite level is a good objective marker of long-term adherence.[11] Using a single cutoff value of active metabolite 6-TGN may not be helpful as there is a lot of variability in its level even among children with wild-type TPMT and NUDT15 genotype.[12] Hierarchical cluster analysis of RBC 6-MP metabolite level has been shown as good method for picking up children with poor adherence.[13] It is recommended that both objective and subjective methods should be used to better assess adherence to 6-MP.[8,9] In this first study from India, we aimed to estimate prevalence of nonadherence to 6-MP in children with ALL by using both subjective and objective methods. We also aimed to study the effect of simple intervention like use of smart pill box in improving adherence to 6-MP during maintenance phase chemotherapy.

Materials and Methods

This was a prospective interventional study conducted in the pediatric oncology clinic of a tertiary care hospital, over a duration of 1 year, after obtaining ethical clearance from the institutional review board.

Participants

A total of 40 newly diagnosed children with ALL between 0 and 18 years of age, who had completed at least 1 month of maintenance chemotherapy according to the Indian Collaborative Childhood Leukemia protocol were enrolled in the study, after taking informed consent from their parents and assent from children more than 12 years. The children who had received blood transfusion in the 2 months prior to the enrollment, or those in whom 6-MP was withheld for more than 5 days due to 6-MP-related toxicities, were excluded from the study. Clinical, demographic, and laboratory data, which included complete blood count and liver function test of the recruited children, were noted and *TPMT* and *NUDT15* mutation analysis was done by gene sequencing for mutant alleles as per standard guidelines.[14]

Assessment of Adherence to 6-MP

Adherence was assessed first by the subjective method by Morisky Medication Adherence Scale (MMAS-8).[15] Parents of the subjects were interviewed as per the questionnaire in MMAS-8 (►**Annuexure 2, 3** and **5**, available in the online version). The total score range on the MMAS-8 was 0 to 8. Children with scores of more than 7.2, between 6 and 7.2 and less than 6 were classified as having high, medium, and low adherence, respectively.[8] Following this, objective assessment of adherence was done by cluster analysis of RBC 6-MP metabolites, 6-TGN, and 6 MMP.[16,17] Briefly, 4 mL blood was collected from each patient and RBCs were cryopreserved at –80°C until analysis of 6-TGN and 6-MMP by mass spectroscopy. Cryopreserved packed RBCs were suspended in 500 µL in peripheral blood smear, and 250 µL of the solution was dispensed into a 1.5-mL microfuge tube. The hydrolysis and extraction process were performed as follows: diluted RBC solution (250 µL) was mixed with 20 µL of isotonic saline, 20 µL of 1.1 M dithiothreitol, and 50 µL of distilled water, vortexed for 30 seconds, and spun down. Then, 34 µL of 70% perchloric acid was added, vortexed for 30 seconds, and centrifuged at 3,000 × *g* for 15 minutes at room temperature. The supernatant (220 µL) was transferred to another polypropylene tube and hydrolyzed at 100°C for 1 hour. After cooling at room temperature, the acidic solution was neutralized with 220 µL of sodium hydroxide. Then, 50 µL of this solution was transferred to 1.5 mL of microfuge tube and dried using Speed Vacuum (Thermofisher Scientific, Cat. No. SPD1030-230) at low energy for 30 to 35 minutes. Samples pellets were then resuspended using 50 µL methanol:water (1:1, water:methanol) mixture for injection. Ultra-high performance liquid chromatography-mass spectrometry analysis was performed using a Dionex Ultimate 3000. Ultra-high performance liquid chromatography chromatographic system combined with a Q Exactive mass spectrometer fitted with a heated electrospray source operated in the positive ion mode. The software interface was Xcalibur 4.2, SII 1.3, and MSTune 2.8 SP1 (Thermo Fisher Scientific, Breda, The Netherlands). The levels of 6-TGN and 6-MMP in the samples were calculated on the basis of comparison of peak intensities with that of the internal standards.[18]

Intervention

Parents and children more than 10 years of age were educated regarding adherence to 6-MP and they were provided with I-store medicine storage box (smart pill box) with inbuilt alarm for a duration of 60 days. The smart pill box had a display for time with a facility to schedule three alarm timings and four compartments to keep the medications. This alarm box acted as a reminder for the patients to take the medication at the scheduled time. For assessment of the impact of intervention, the patients were again subjected to subjective and objective measurement of adherence by MMAS-8 and 6-MP metabolite level measurement as described before.

Primary Outcomes

To estimate the prevalence of nonadherence to 6-MP in maintenance phase chemotherapy and assess the impact of smart pill box as simple cost-effective intervention for improving adherence to 6-MP in maintenance phase chemotherapy in pediatric ALL.

Secondary Outcomes

1. To assess effectiveness of MMAS-8 as a subjective method for assessing adherence and its correlation with the objective method of estimating drug metabolite levels.
2. To look for NUDT and TPMT polymorphism in children with ALL and there correlation with the metabolite levels.
3. To study the factors affecting adherence in children with ALL.

Inclusion Criteria

Newly diagnosed children with ALL who had completed at least 1 month of maintenance chemotherapy.

Exclusion Criteria

1. Patients in last 3 months of maintenance phase.
2. Patients for whom 6-MP was withheld for more than 5 days by treating physician due to any reason during previous 1 month.
3. Patients who received RBC transfusion in the last 90 days.
4. Children with relapsed ALL.
5. Patients not consenting for the study.

Statistical Analysis

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Categorical outcomes were compared between study groups using the chi-square test and/or Fisher's exact test. Categorical variables at different time periods of follow-up were compared using the McNamar test; reported frequencies and proportions along with *p*-values. For normally distributed quantitative parameters, the mean values were compared between study groups using independent sample *t*-test (two groups). The change in the quantitative parameters, before and after the intervention was assessed by paired *t*-test. For normally distributed quantitative parameters, the mean values were compared between study groups using analysis of variance. For nonnormally distributed quantitative parameters, medians and interquartile range (IQR) were compared between study groups using the Mann–Whitney *U* test. The change in the quantitative parameters, before and after the intervention was assessed by Wilcoxon signed-rank test. For nonnormally distributed quantitative parameters, medians and IQR were compared between study groups using the Kruskal–Wallis test. Two numerical parameters (6-TGN and 6-MMP levels) were used to perform cluster analysis by hierarchical agglomerative method. Cluster 1 were characterized by very low levels (above 20th percentile of cutoff point) of 6-TGN levels and 6-MMP levels and these were considered to be nonadherent and other three clusters were considered adherent. A *p*-value of < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis. The mean score of MMAS-8 were calculated and the pre- and postintervention mean scores were compared by using the chi-square test. The hierarchical cluster analysis of drug metabolite concentrations was done and the pre- and postintervention levels were compared. Correlation between MMAS-8 and metabolite levels was done and *p*-value was calculated.

Ethical Approval

IEC, JNMC, Belgaum; No. MDC/DOME/161 dated January 25, 2021. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All authors approved the final manuscript.

Results

A total of 40 children with ALL in complete remission 1 (CR1), who had completed at least 1 month of maintenance phase of chemotherapy were enrolled in the study. The mean age was 7.39 ± 4.29 years and male-to-female ratio was 1.5:1. B-cell ALL was the most common immunophenotype of ALL accounting for 87.50% of the cases. As per the National Cancer Institute risk stratification, 55% belonged to standard risk and 45% to high risk. As far as distribution of patients in different maintenance cycle was concerned, 32.50, 20.00, 5.00, 10.00, 15.00, 7.50, and 10% belonged to M1, M2, M3, M4, M5, M6, and M7 number of maintenance cycles, respectively. Evaluation of *NUDT15* and *TPMT* polymorphisms revealed presence of NUDT15*3 polymorphism in heterozygous state in 4 out of 39 (10.26%) patients, and none had *TPMT* polymorphism (►**Table 5**).

The baseline subjective assessment of adherence to 6-MP by MMAS-8 revealed that 3 children (7.5%) had low adherence, 17 (42.5%) had medium adherence, and 20 (50%) had high adherence (►**Table 1**). Objective assessment of baseline adherence was done by quantifying 6-TGN and 6MMP levels and subjecting them to cluster analysis. Cluster 1 consisted of those with very low 6-MMP and very low 6-TGN levels, cluster 2 included those with low 6-MMP and low 6-TGN, cluster 3 consisted of those with medium 6-MMP and low 6-TGN, and cluster 4 included those with low 6-MMP and high 6-TGN levels (►**Fig. 1**). Cluster analysis revealed that 4 (10%) had very low 6-TGN and 6-MMP levels reflecting poor

Table 1 Descriptive analysis of baseline MMAS-8 in the study population ($N = 40$)

MMAS-8	Frequency	Percentage
High adherence (> 7.2)	20	50
Medium adherence (6–7.2)	17	42.50
Low adherence (< 6)	3	7.50

Abbreviation: MMAS-8, Morisky Medication Adherence Scale 8.

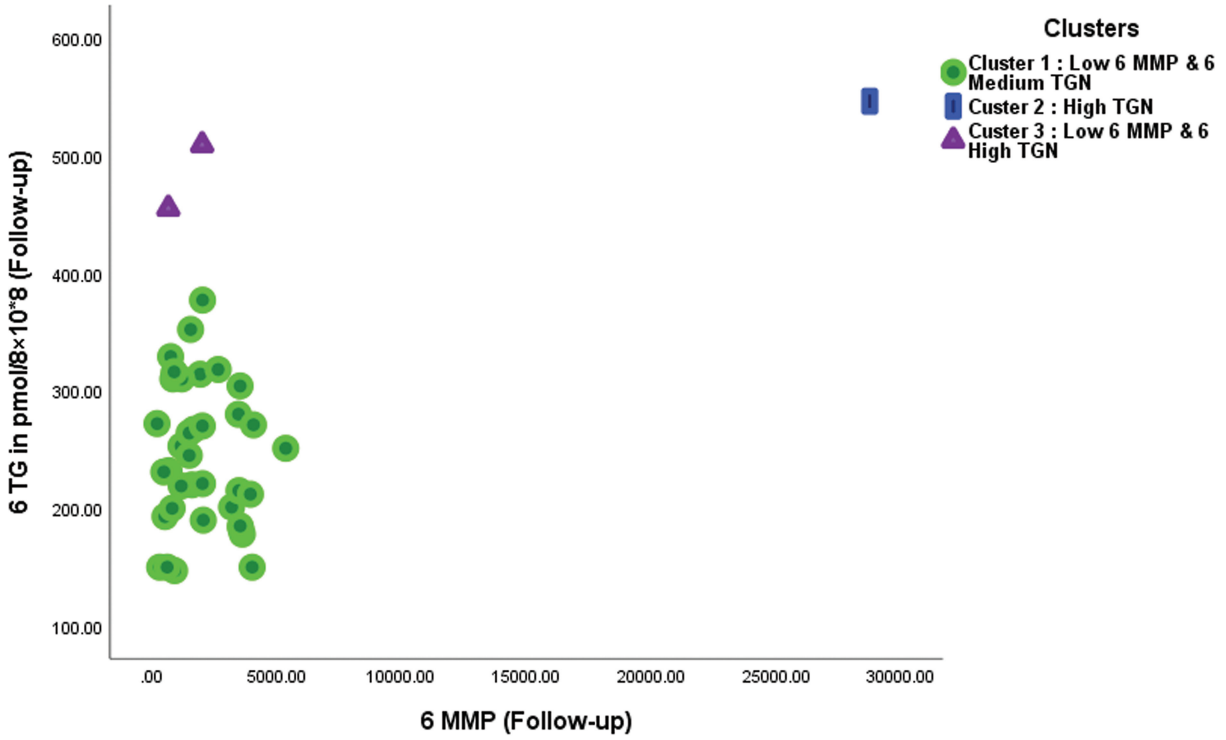

Fig. 1 Scatter plot showing the clusters for 6-methylmercaptopurine (6-MMP) and 6-thioguanine (6-TGN) follow-up levels.

adherence (►**Fig. 2**). The baseline mean MMAS-8 score was 7.34 ± 0.78 and the baseline median 6-TGN and 6-MMP levels were 150 (100, 221) and 879 (270, 1528) pmol/8×10^8 RBCs, respectively. There was no statistically significant association of baseline adherence with patient- or parent-related factors (►**Table 2**).

The assessment of adherence by MMAS-8 and RBC 6-TGN and 6-MMP levels after the intervention with smart pill box showed statistically significant impact of intervention on improving the adherence. Following the intervention, MMAS-8 results illustrated that none had low adherence, 11 (27.5%) had medium adherence, and 29 (72.5%) had high

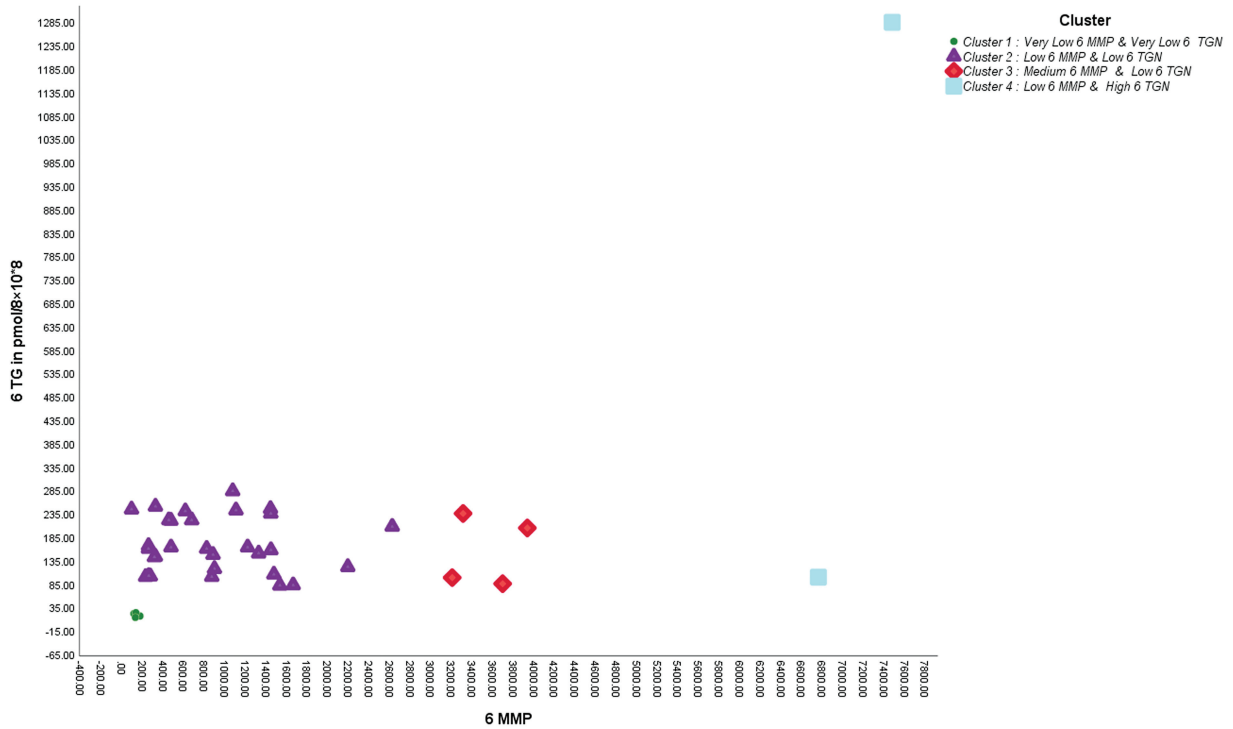

Fig. 2 Scatter plot showing the clusters for 6-methylmercaptopurine (6-MMP) and 6-thioguanine (6-TGN) baseline levels.

Table 2 Comparison between gender, number of siblings, and socioeconomic status, type of family, and education (mother and father) with Morisky scale (parent) baseline in the study population ($N = 40$)

Parameter	MMAS-8 baseline			Chi-square value	*p*-Value
	High adherence ($N = 20$)	Medium adherence ($N = 17$)	Low adherence ($N = 3$)		
Gender					
Male	11 (55.00%)	10 (58.82%)	3 (100.00%)	–	*
Female	9 (45.00%)	7 (41.18%)	0 (0.00%)		
Number of siblings					
Zero	0 (0.00%)	2 (11.76%)	0 (0.00%)	–	*
One	11 (55.00%)	9 (52.94%)	0 (0.00%)		
Two	6 (30.00%)	5 (29.41%)	3 (100.00%)		
Three	3 (15.00%)	1 (5.88%)	0 (0.00%)		
Socioeconomic status (as per modified B.G. Prasad classification[30])					
I	3 (15.00%)	1 (5.88%)	0 (0.00%)	–	*
II	2 (10.00%)	3 (17.65%)	0 (0.00%)		
III	4 (20.00%)	3 (17.65%)	1 (33.33%)		
IV	2 (10.00%)	7 (41.18%)	2 (66.67%)		
V	9 (45.00%)	3 (17.65%)	0 (0.00%)		
Type of family					
Joint	9 (45.00%)	6 (35.29%)	2 (66.67%)	1.13	0.5686
Nuclear	11 (55.00%)	11 (64.71%)	1 (33.33%)		
Education (mother)					
No formal education	3 (15.00%)	0 (0.00%)	0 (0.00%)		
Primary education	2 (10.00%)	6 (35.29%)	2 (66.67%)	–	*
Secondary education	11 (55.00%)	9 (52.94%)	1 (33.33%)		
Graduate	4 (20.00%)	2 (11.76%)	0 (0.00%)		
Postgraduate	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Education (father)					
No formal education	3 (15.00%)	1 (6.25%)	0 (0.00%)	–	*
Primary education	3 (15.00%)	3 (18.75%)	1 (33.33%)		
Secondary education	7 (35.00%)	9 (56.25%)	1 (33.33%)		
Graduate	7 (35.00%)	2 (12.50%)	1 (33.33%)		
Postgraduate	0 (0.00%)	1 (6.25%)	0 (0.00%)		

Abbreviation: MMAS-8, Morisky Medication Adherence Scale 8.
*No test applicable due to the nature of the data.

adherence (►**Table 3**). The mean MMAS-8 significantly improved to 7.66 ± 0.55 (p-value < 0.015) after the intervention and the median 6-TGN level improved to 253 pmol/8×10^8 RBCs (p-value < 0.001) as shown in ►**Table 4**. Similarly, on cluster analysis, there was no cluster of patients with very low 6-TGN and 6-MMP levels (►**Fig. 1**). The correlation between the 6-MMP levels and the liver enzymes was not statistically significant.

Table 3 Descriptive analysis of follow-up MMAS-8 in the study population ($N = 40$)

MMAS-8 (follow-up)	Frequency	Percentage
High adherence	26	65.00
Medium adherence	14	35.00

Abbreviation: MMAS-8, Morisky Medication Adherence Scale 8.

Discussion

The subject of nonadherence to 6-MP in pediatric ALL has been well studied in developed countries; nonadherence leads to significant increase in relapse risk.[8,11,19,20] In the first Indian study exploring adherence to 6-MP in children with ALL, we utilized both subjective and objective methods, as only subjective method of parent or child interview is

Table 4 Comparison of MMAS-8, 6-TGN, and 6-MMP levels at baseline and 2 months after intervention

Parameter	Mean ± SD	Mean difference	*p*-Value
Morisky scale parent score ($N = 40$)			
Baseline	7.34 ± 0.78	−0.32	0.015
Follow-up	7.66 ± 0.55		
6-TGN in pmol/8 × 10^8 RBC	**Median (interquartile range)**	**Wilcoxon's sign rank test statistics**	***p*-Value**
Baseline	150 (121)	−4.80	< 0.001
Follow-up	253 (114)		
6-MMP in pmol/8 × 10^8 RBC			
Baseline	879 (1258)	−3.82	< 0.001
Follow-up	1678 (2593)		

Abbreviations: 6-MMP, 6-methylmercaptopurine; 6-TGN, 6-thioguanine; MMAS-8, Morisky Medication Adherence Scale 8; RBC, red blood cell; SD, standard deviation.

Table 5 Comparison of mean of 6-TGN in pmol/8 × 10*8 (baseline) and 6-MMP (baseline) between NUDT mutation ($N = 39$)

Parameter	NUDT mutation (mean ± SD)		*p*-Value
	Positive ($N = 4$)	Negative ($N = 35$)	
6-TGN in pmol/8 × 10*8 (baseline)	177.25 ± 42.95	220.21 ± 252.87	0.739
6-MMP (baseline)	499.75 ± 262.27	1670.64 ± 1719.99	0.187

Abbreviations: 6-MMP, 6-methylmercaptopurine; 6-TGN, 6-thioguanine; SD, standard deviation.

likely to overestimate adherence.[21,22] Indeed, only 3 out of 40 (7.5%) children were found to have low adherence (< 75%) by MMAS-8 at baseline, while RBC metabolites cluster analysis identified one more child (4 out of 40) with poor adherence to 6-MP. Our finding of 17 out of 40 children having medium level of adherence (75–90%) is of particular concern. Overall, 40% of children were found to have adherence below 90% by MMAS-8. We could not identify separate RBC metabolite cluster for children with medium adherence measured by MMAS-8, probably because they were part of large cluster 2 consisting of 30 patients with low 6-TGN and 6-MMP levels. It is possible that all these children in cluster 2 were at increased risk of nonadherence as suggested by Bhatia et al.[8] Alternatively, low RBC metabolite levels could be explained by ethnicity and pharmacogenomics.[23,24] We need larger study to establish RBC metabolite levels, during 6-MP maintenance therapy in Indian children with ALL. In our cohort, we did not find any patient with *TPMT* polymorphism; however, 4 out of 39 patients tested positive for *NUDT15**3 polymorphism in heterozygous state. This is in line with similar prevalence in other Indian studies.[12,25] None of the factors studied influenced adherence in our cohort. This is in contrast with larger COG study which found ethnicity and socioeconomic factors as significantly associated with adherence.[8] Our finding of lack of association with these factors could be because of smaller sample size and most of the patients belonging to similar ethnic background. Various interventions have been studied to improve adherence to medications which are used chronically with conflicting results.[26,27] In particular, interventions like mobile text reminders, alarms, and parental education have failed to improve adherence in children on 6-MP maintenance therapy.[26] However, our simple, affordable, smart pill box with inbuilt alarm significantly improved adherence in our cohort as measured by both methods. Notably, none of the patient showed poor (< 75%) adherence after the intervention. Both the MMAS-8 and median 6-TGN level significantly increased after the use of smart pill box for 2 months. This positive effect on adherence could be in part due to higher number of patients with low and medium adherence at baseline. This finding is of particular relevance to children from LMIC as it may help in reducing relapse risk and overall survival, as very few children with relapse undergo curative treatment like transplant or novel therapies like immunotherapy due to inadequate access and financial constraints.[28,29] In this study, we found high prevalence of NUDT polymorphism, which can contribute to severe toxicity due to 6-MP. Hence, NUDT and TPMT studies can be done upfront, so that the 6-MP dose can be adjusted during consolidation itself, thus leading to reduced morbidities and mortalities due to 6-MP toxicity. Also, dose adjustment depending on NUDT and TPMT polymorphism would prevent interruption of chemotherapy, eventually improving the outcome.

Limitations

Our study is limited by small sample size and lack of measurement of adherence at multiple time points during maintenance treatment.

Conclusion

This study also highlights the fact that nonadherence to 6-MP is widely prevalent in Indian children during maintenance treatment for ALL and simple measures like smart pill box can improve adherence and more such approaches should be studied in LMIC setting. We did not find any factor that had significantly affected the adherence of the children.

What is Already Known?

The issue of nonadherence to 6-MP and the consequent increased risk of relapse is well studied in western countries.

What this Study Adds?

1. This is the first Indian study to assess nonadherence by subjective and objective methods.
2. This study emphasizes the fact that simple intervention by smart pill box can significantly reduce nonadherence.

Patient Consent
Informed patient consent was obtained for this study.

Funding
None.

Conflict of Interest
None declared.

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References

1 Pui CH, Evans WE. A 50-year journey to cure childhood acute lymphoblastic leukemia. Semin Hematol 2013;50(03): 185–196
2 Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Lancet 2013;381(9881):1943–1955
3 Pui C-H, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood 2012;120(06):1165–1174
4 Colunga-Pedraza PR, Colunga-Pedraza JE, Peña-Lozano SP, Gómez-De León A, Ruiz-Delgado GJ, Ribeiro RC. Diagnosis and treatment of acute lymphoblastic leukemia in Latin America. Hematology 2022;27(01):971–976
5 Brandalise SR, Viana MB, Pinheiro VR, et al. Shorter maintenance therapy in childhood acute lymphoblastic leukemia: the experience of the prospective, randomized Brazilian GBTLI ALL-93 Protocol. Front Pediatr 2016;4:110
6 Toksvang LN, Lee SHR, Yang JJ, Schmiegelow K. Maintenance therapy for acute lymphoblastic leukemia: basic science and clinical translations. Leukemia 2022;36(07):1749–1758
7 Teachey DT, Hunger SP, Loh ML. Optimizing therapy in the modern age: differences in length of maintenance therapy in acute lymphoblastic leukemia. Blood 2021;137(02):168–177
8 Bhatia S, Landier W, Hageman L, et al. 6MP adherence in a multiracial cohort of children with acute lymphoblastic leukemia: a Children's Oncology Group study. Blood 2014;124(15): 2345–2353
9 Kahn JM, Stevenson K, Beauchemin M, et al. Oral mercaptopurine adherence in pediatric acute lymphoblastic leukemia: a survey study from the Dana-Farber Cancer Institute acute lymphoblasticleukemia consortium. J Pediatr Hematol Oncol Nurs 2023;40 (01):17–23
10 Chotsampancharoen T, Songthawee N, Chavananon S, Sripornsawan P, McNeil EB. Relapsed childhood acute lymphoblastic leukemia: experience from a single tertiary center in Thailand. Asian Pac J Cancer Prev 2022;23(10):3517–3522
11 Landier W. Adherence to oral chemotherapy in childhood acute lymphoblastic leukemia: an evolutionary concept analysis. Oncol Nurs Forum 2011;38(03):343–352
12 Khera S, Trehan A, Bhatia P, Singh M, Bansal D, Varma N. Prevalence of TPMT, ITPA and NUDT 15 genetic polymorphisms and their relation to 6MP toxicity in north Indian children with acute lymphoblastic leukemia. Cancer Chemother Pharmacol 2019;83 (02):341–348
13 Hawwa AF, Millership JS, Collier PS, et al. The development of an objective methodology to measure medication adherence to oral thiopurines in paediatric patients with acute lymphoblastic leukaemia–an exploratory study. Eur J Clin Pharmacol 2009;65(11): 1105–1112
14 Gong L, Whirl-Carrillo M, Klein TE. Pharm GKB, an integrated resource of pharmacogenomic knowledge. Curr Protoc 2021;1 (08):e226
15 Moon SJ, Lee WY, Hwang JS, Hong YP, Morisky DE. Accuracy of a screening tool for medication adherence: A systematic review and meta-analysis of the Morisky Medication Adherence Scale-8. PLoS One 2017;12(11):e0187139
16 Jaeger A, Banks D. Cluster analysis: a modern statistical review. Wiley Interdiscip Rev Comput Stat 2022;•••:e1597
17 Alsous M, Abu Farha R, Alefishat E, et al. Adherence to 6-mercaptopurine in children and adolescents with acute lymphoblastic leukemia. PLoS One 2017;12(09):e0183119
18 Moon SY, Lim JH, Kim EH, et al. Quantification of thiopurine nucleotides in erythrocytes and clinical application to pediatric acute lymphoblastic leukemia. Ther Drug Monit 2019;41(01): 75–85
19 Kondryn HJ, Edmondson CL, Hill J, Eden TO. Treatment nonadherence in teenage and young adult patients with cancer. Lancet Oncol 2011;12(01):100–108
20 Toksvang LN, Als-Nielsen B, Bacon C, et al. Thiopurine Enhanced ALL Maintenance (TEAM): study protocol for a randomized study to evaluate the improvement in disease-free survival by adding very low dose 6-thioguanine to 6-mercaptopurine/methotrexate-based maintenance therapy in pediatric and adult patients (0-45 years) with newly diagnosed B-cell precursor or T-cell acute lymphoblastic leukemia treated according to the intermediate risk-high group of the ALLTogether1 protocol. BMC Cancer 2022; 22(01):483
21 Biressaw S, Abegaz WE, Abebe M, Taye WA, Belay M. Adherence to Antiretroviral Therapy and associated factors among HIV infected children in Ethiopia: unannounced home-based pill count versus caregivers' report. BMC Pediatr 2013;13:132
22 Pearce CJ, Fleming L. Adherence to medication in children and adolescents with asthma: methods for monitoring and intervention. Expert Rev Clin Immunol 2018;14(12):1055–1063
23 Matimba A, Li F, Livshits A, et al. Thiopurine pharmacogenomics: association of SNPs with clinical response and functional validation of candidate genes. Pharmacogenomics 2014;15(04): 433–447

24 Lim SZ, Chua EW. Revisiting the role of thiopurines in inflammatory bowel disease through pharmacogenomics and use of novel methods for therapeutic drug monitoring. Front Pharmacol 2018;9:1107
25 Kodidela S, Dorababu P, Thakkar DN, et al. Association of NUDT15 c. 415C> T and FPGS 2572C> T variants with the risk of early hematologic toxicity during 6-MP and low-dose methotrexate-based maintenance therapy in Indian patients with acute lymphoblastic leukemia. Genes (Basel) 2020;11(06):594
26 Bhatia S, Hageman L, Chen Y, et al. Effect of a daily text messaging and directly supervised therapy intervention on oral mercaptopurine adherence in children with acute lymphoblastic leukemia: a randomized clinical trial. JAMA Netw Open 2020;3(08): e2014205
27 Skrabal Ross X, Gunn KM, Patterson P, Olver I. Mobile-based oral chemotherapy adherence-enhancing interventions: scoping review. JMIR Mhealth Uhealth 2018;6(12):e11724
28 Bhojwani D, Pui CH. Relapsed childhood acute lymphoblastic leukaemia. Lancet Oncol 2013;14(06):e205–e217
29 Jabeen K, Ashraf MS, Iftikhar S, Belgaumi AF. The impact of socioeconomic factors on the outcome of childhood acute lymphoblastic leukemia (ALL) treatment in a low/middle income country (LMIC). J Pediatr Hematol Oncol 2016;38(08): 587–596
30 Debnath DJ, Kakkar R, Modified BG. Prasad Socio-economic Classification, updated – 2020. Indian J Community Health 2020;32:124–125

