"ASSESSMENT OF ADHERENCE TO 6-MERCAPTOPURINE IN MAINTENANCE PHASE CHEMOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA- A PROSPECTIVE INTERVENTIONAL STUDY"

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"ASSESSMENT OF ADHERENCE TO 6-MERCAPTOPURINE IN MAINTENANCE PHASE CHEMOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA – A PROSPECTIVE INTERVENTIONAL STUDY ", is ethical and justifiable.** The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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ABSTRACT

Background and aims

6 mercaptopurine (MP) forms backbone of maintenance chemotherapy for ALL, which typically lasts for 2 to 2.5 years. As with any long-term therapy, poor adherence is serious impediment in 6 MP maintenance treatment, which may impact outcome. Indeed, COG study found 3.9 fold increased risk of relapse in children with 6 MP adherence of less than 90%. There are no studies regarding adherence to 6MP from India. Hence, we studied prevalence of non- adherence to 6 MP and impact of use of electronic pill box on it, in our cohort on maintenance chemotherapy.

Methods

In this prospective cohort study, we included children who have completed at least 1 month of maintenance chemotherapy. At baseline, adherence was measured subjectively by Morisky score and objectively by measurement of 6 thioguanine (TGN) and 6 methylmercaptopurine (MMP) levels. Subsequently, they were provided with I store medicine storage box with inbuilt alarm. Measurement of adherence was repeated after 2 months.

Results

40 children were enrolled, with mean age of 7.39 +- 4.29 years. At baseline, 20, 17 and 3 children were categorized as having high, intermediate and poor adherence, respectively, based on Morisky score.The median 6 TGN and 6 MMP levels at baseline were 150 with IQR of 100 to 221 and 825 with IQR of 900 to 3553, respectively. On cluster analysis, 4 children were found to have poor adherence. After the intervention, there was statistically significant increase in adherence measured by both methods. Mean Morisky score improved to 7.66 +- 0.55 (p value of 0.015) after

the intervention. Similarly, median 6 TGN level was significantly higher at 253 (p value < 0.001), post intervention.

Conclusion

Non- adherence to 6 MP is significant problem in children on maintenance chemotherapy for ALL. Smart pill box can be a cheap and effective way of improving adherence.

LIST OF ABBREVIATIONS	
ALL	Acute Lymphoblastic Leukaemia
6MP	6 Mercaptopurine
MTX	Methotrexate
6TGN	6 Thioguanine nucleotide
TPMT	Thiopurine S-methyltransferase
RBC	Red Blood Cell
MMAS	Morisky Medication Adherence Scale
FAB	French American British
WBC	White Blood Cell
BM	Bone Marrow
AML	Acute Myeloid Leukemia
NSE	Neuron specific Enolase
MPO	Myeloperoxidase
SB	Sudan Black
CD	Cluster of differentiation

LAP	Leucocyte Alkaline Phosphatase
LP	Lumbar Puncture
HIC	High Income Country
LMIC	Low and middle income countries
ANC	Absolute Neutrophil Count
MMP	Methylated mercaptopurine
IQR	Interquartile Range
ITPA	Inosine triphosphate Pyrophosphatase
NUDT	Nudix Hydrolase
NCI	National Cancer Institute
COG	Children’s Oncology Group
MRD	Minimal Residual Disease

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a malignant neoplasm of lymphoblast. It is the most common malignancy among pediatric age group. As per literature review, ALL affects more whites than black, males more than females and it is more prevalent in the western countries than in developing countries[1].

Worldwide annual number of new cases of childhood cancer exceeds 2 million. In India more than 75,000 cases of pediatric cancers are diagnosed every year. Acute Lymphoblastic leukemia accounts for approximately 77% of cases of childhood leukemia[1.] Approximately 50,000 cases of Leukemia are diagnosed in India every year[2].

ALL being the most common type of cancer in childhood, was considered fatal until 1960s. There is enormous progress in the treatment of childhood cancer, mainly in the developed countries. The 5-year survival rate of pediatric ALL is more than 90% in high income country (HIC)[3,4.] In India it is seen that survival rates of ALL has improved from 20% to 60%. Diagnostic and treatment modalities for ALL have seen tremendous advancements over the past few decades. Despite a high incidence, and constant rise in pediatric cancers in the developed countries, their success stories are ample[5].

In India, majority of the treatment option are stationed in major cities of the country resulting in decreased accessibility and feasibility of the treatment adequately for the patients in peripheries. Some of the modifiable factors responsible for poor outcome are cultural barriers, malnutrition, poor socioeconomic conditions and delay in diagnosis and referral. Factors like high baseline WBC counts, age, extra medullary

disease, poor cytogenetics and pre-treatment with steroids, result in adverse effect on the treatment outcome[6].

Treatment of ALL consists of 5 phases, which includes, Induction, Consolidation, Interim maintenance, Delayed intensification, and Maintenance. First phase which is also called as remission induction, involves treatment for 4 weeks. Induction phase aims to eradicate the malignant cells from the bone marrow thus restoring normal hematopoesis. Second phase called as consolidation phase is directed towards intensive CNS therapy along with systemic therapy to remove the residual malignant cells and to prevent CNS relapse. This is followed by the interim maintenance phase and delayed intensification. The last, longest and one of the most important phases of treatment is the maintenance phase which last for 2-2.5 years. This phase is targeted towards the eradication of leukemic stem cell by maintaining adequate myelosuppression and alteration of tumor microenvironment, thus reducing the chances of relapse[1] . Maintenance phase consists of daily oral dose of 6 mercaptopurine (6MP), weekly oral dose of methotrexate (MTX) and monthly pulses of dexamethasone and vincristine[1].

After the completion of induction phase chemotherapy, almost 95% of the cases undergo remission but 20% of cases may relapse and adequate adherence to maintainence chemotherapy is of paramount importance in reducing the chances of relapse[7]. Maintenance phase is a prolonged phase requiring self or parent administration of oral antimetabolite chemotherapy [8]. Systemic exposure to oral antimetabolite that is 6-mercaptopurine is a critical component in maintenance phase chemotherapy[8]. Potential determinants for adequate systemic 6MP exposure are pharmacogenetics, bioavailability, and adherence to daily oral administraton[8].

One of the important factors contributing to lower cure rate in developing countries compared to developed countries is non adherence to the oral medications in the maintenance phase of chemotherapy. Children with poor compliance in the maintenance phase are found to have 3.9 fold increased risk of relapse[7]. There is ample literature supporting the fact, that patients with low erythrocyte levels of metabolites of 6-MP namely 6 thioguanine (6-TGN) of less than 95% have higher incidence of relapse[9].

Adherence to 6MP can be estimated by direct, indirect and surrogate measures. The direct measures include, red blood cell assays of 6MP metabolites which consist of 6 thioguanine (6TGN) nucleotide, Methylated mercaptopurine and 6-methylthioinosine monophosphate[8] . The RBC levels of these metabolites will have differing patterns of concentration in adherent versus nonadherent patients.

Surrogate measures ,include white blood count or neutrophil count[8],as well as behavioral observations like pill counts and electronic medication-monitoring devices[8].Indirect measurements of adherence can be done by patient and/or parent self-report , questionnaires, adherence scales, interviews, and diaries[8].

6-MP drug has short half-life of 1.5hrs, so its measurement to assess the drug levels cannot be done[10]. The intracellular metabolism of 6-MP depends on the activity of thiopurine-S-methyltransferase enzyme (TPMT) which is subjected to genetic polymorphism with an inverse correlation between 6-TGNs levels and TPMT activity[10].However its intracellular metabolite 6-thioguanine and 6-methyl mercaptopurine begins to appear in RBC by 2-3 weeks. The measurement of the concentration of these metabolites is essential in therapeutic drug monitoring and is considered as a good long term indicator[10].

Smart pill box is an electronic device with an alarm to remind the patient and the parent to give the medication on time. This can increase the adherence to oral medication thus reducing chances of relapse among the patients of ALL. Education of the patient and the parents regarding the importance of adherence and the correct method of administration of the drug also plays a very important role in improving the adherence and eventually resulting in better treatment outcome. There is paucity of literature regarding the measures to assess and to improve adherence to maintenance chemotherapy from developing world where the treatment outcome is relatively inferior. Hence we took up this study with the aim to assess adherence by Morisky Medication Adherence Scale (MMAS) and 6MP metabolite levels. We also aim to study the impact of intervention in the form of smart pill box and patient and parent education in improving the adherence.

OBJECTIVES

PRIMARY OBJECTIVES:

1. To assess baseline adherence to 6-Mercaptopurine(6MP) during maintenance phase chemotherapy in children undergoing treatment for Acute Lymphoblastic Leukaemia (ALL) and to evaluate the impact of smart pill box and parent education in improving the adherence

SECONDARY OBJECTIVES:

1. To identify factors that influence adherence to 6-MP in children with ALL.
2. To compare subjective method using Morisky medication adherence scale (MMAS-8) with objective method using 6-MP metabolite levels in assessing the adherence.
3. To study the pattern of Thiopurine methyl transferase (TPMT) genotype in the given cohort and to correlate it with 6MP metabolite level.

REVIEW OF LITERATURE

Acute lymphoblastic leukemia(ALL) is the malignant neoplasm seen in the precursor cells of lymphocytes, it is the most common malignancy among pediatric age group. Worldwide annual number of new cases of childhood cancer exceeds 2 million. In India more than 75,000 cases of pediatric cancers are diagnosed every year. Acute Lymphoblastic leukemia accounts for approximately 77% of cases of childhood leukemia[1].

Incidence of leukemia in children appears to be increasing ,a study conducted in Great Britain showed that the incidence increased from 38 per million to 46 per million when compared between 1971-1975 and 1996-2000 respectively[11] and among the European population it was found that there was increase in the incidence by 1.4 percent per year from 1970-1999[12] further in the analysis conducted by SEER data base done from 2000-2016 ,there in average increase in the annual incidence by approximately 1% [13] .This increase in the incidence also reflects about accurately reporting the disease. In majority of the cases the cause for ALL is not known, but with increase in incidence some studies have shown some environmental and genetic risk associations. There were large studies which have showed that there was increase in incidence of ALL in children who were associated with advanced paternal age and maternal fetal loss[14,15,16]. Inconsistent results were seen in studies showing relationship between leukemia and rural/urban status, possible environmental exposures, population density [17] .ALL is not considered as a familial disease but it was seen in studies that when compared to the general population, the monozygotic twins siblings of the children with ALL were at higher risk of developing ALL[18] .While some genetic syndromes are associated with increased risk of ALL like

Down's syndrome, Bloom syndrome, neurofibromatosis type 1, ataxia telangiectasia [19,20] .Apart from these some polymorphic variants of the gene encoding IKAROS (CDKN2A,ARID5B, and IKZF1) were also associated with increased risk of leukemia and along with these some germ line mutations like ETV6,TP53,PAX5 act as predisposing factors for the development of ALL[21-25].

ALL was seen more in whites than black, males more than females, more in the western countries than in developing countries[1]. In some of the studies it was found that the peak in the incidence of ALL was between the age group of 2 to 5 years[26-29].

ALL being the most common type of cancer in childhood, was considered fatal until 1960s.There is enormous progress in the treatment of childhood cancer, mainly in the developed countries. As per current literature, this disease has a 5-year survival rate of more than 90% in HIC today[3,4]. However in developing countries, the survival rate is around 60-70%. In India, survival rates of ALL has improved from 20% to 60%[30]. Diagnostic and treatment modalities for ALL have seen tremendous advancements over the past few decades.

In the past 50 years treatment of children with acute lymphoblastic leukemia has significantly improved. This success story of cancer treatment is measured by improvement in the survival rate from less than 10% to now more than 80% in recent reports[3].

The opening of the era of the chemotheraphy was in 1948 with the transient remissions achieved by Aminopterin[31].In 1971 approximately 50% of the patients were cured by combination therapy and effective CNS directed therapy[32].Whereas in 1981 improvement in the outcome was seen by re-induction[33]and in 1982 it was found

that triple intrathecal therapy that is with methotrexate, hydrocortisone and cytarabine can be an effective substitute for some patients who require prophylactic cranial irradiation[34].Further, in 1983, a significant improvement in the outcome was achieved after the introduction of the weekly high dose of L asparaginase[35] and in the same year systemic and testicular relapses were decreased by the addition of high dose methotrexate with leucovorin rescue[36].In 1995, it was discovered that mercaptopurine toxicity was influenced by inherited genetic polymorphism in encoding the gene of TPMT[37].In 2009, for all the patients prophylactic cranial irradiation was eliminated with effective systemic chemotherapy and intrathecal chemotherapy[38]. An important milestone was achieved in 2009 when targeted therapy in the form of tyrosine kinase inhibitor namely Imatinib was introduced for the treatment of Philadelphia chromosome –positive ALL. These were the important developmental milestones in the treatment of Acute lymphoblastic Leukemia[3].

We have seen drastic improvement in prognosis of children with acute lymphoblastic leukemia between 1960's to 1990's. Current chemotherapy, which includes multiagent regimen, has resulted in 80-90% of patients as relapse free survivors in the long term[39].

Leukemias are classified as Acute and chronic leukemia, Acute leukemia is characterized by clonal proliferation of immature components of the bone marrow. Chronic leukemias are characterized by proliferation of mature components of the bone marrow. The terminology, congenital leukemia is used, if leukemia occurs within 4weeks of life[39].

CLASSIFICATION OF ALL

Morphological classification of ALL, which is devised by FAB (French American British) cooperative group it is mainly done by the appearance of the leukemic blast cells. There are three categories-L1,L2 and L3.L1 will have blast cells which are small in size with high nuclear to cytoplasmic ratio,L2 blasts are larger than L1 with prominent nucleoli and abundant cytoplasm and also show marked variability in the size,L3 lymphoblasts are similar to burkitt lymphoma cells and they also have cytoplasm which is deeply basophilic and a prominent cytoplasmic vacuolization[39].

Immunophenotype classification of ALL is mainly based on the lineage specific and maturation specific antigens, which are present in the cytoplasm and over the cell surface. It is classified into three broad types- B-precursor cell type, mature b cell type and T cell type, and these are associated with distinct features[39].

B-precursor cell is further divided into three types based on intracytoplasmic immunoglobulins and cell surface markers, they are Pro-B cell ALL, early pre B cell ALL, and Pre B ALL. Among these, early pre B cell ALL is the commonest[39].

Pro B cell ALL seen in 3-4% of the pateints, early pre B cell ALL is seen in 60-70% patients and 20-30% of the patients have pre B cell ALL[39].

DIAGNOSIS OF ALL

ALL is mainly a disease involving peripheral blood and bone marrow, in ALL a organ/tissue can be infiltrated by abnormal cells leading to enlargement of spleen /liver or lymphadenopathy[1] ALL can range from being asymptomatic to life threatening complications like infection, hemorrhage or respiratory distress, child can present with fever, pallor, petechia, easy bruising, limp or bony pain (it is secondary

to the stretching of the periosteum or joint capsule due to invasion by leukemic cells)[1]. Meta analysis of 33 studies consisting of >3000 children showed that more than half of the patients with leukemia had one of the following features on presentation: palpable liver, pallor, bruising, fever or palpable spleen and 6% of the patients were asymptomatic[40] .64% had hepatomegaly, 61% had splenomegaly these were the most common and these patients presented with weight loss, abdominal pain ,anorexia, or abdominal distension[40] . More than half of them even presented with lymphadenopathy or fever which could be due to infection or a constitutional symptom of leukemia .43% of the patients have musculoskeletal pain as the presenting complaint and the young children may come with refusal to bear weight or limp mainly due to the bone pain[40]. Half of the patients can even present with the features of anemia and also with bleeding [41] .There are some uncommon manifestations of leukemia like head ache which is seen in less than 5% of the patients, but in case of leukemia involving the central nervous system they can come with other features also, like neck rigidity, vomiting lethargy, cranial nerve abnormalities[42-44] .Less than 1% of the boys can present with testicular enlargement whereas in 10% of the boys testicular involvement is present in relapsed leukemia[45] .One more less common manifestation in case of leukemia is a mediastinal mass, seen mainly in T-ALL, which can further cause superior vena cava syndrome and they come with dyspnea(due to mass compressing the trachea) , pain ,dysphagia, or swelling in the face, neck, or upper limbs due to SVC obstruction[1].

Normally in bone marrow, less than5% of nucleated cells constitute the blast forms and in peripheral blood they are not usually present except in cases of overproduction like in infection, bleeding or BM invasion [1].If more than5% blast

forms are present in marrow and if there is presence of blast cells in peripheral blood then it should raise a suspicion of leukemia[1]

ALL is mainly a disease involving peripheral blood and bone marrow. In ALL, an organ or tissue can be infiltrated by abnormal cells leading to enlargement of extramedullary organs like spleen and/or liver or lymphadenopathy[1] .Peripheral Blood smear can reveal abnormal RBC count, abnormal leucocyte count and thrombocytopenia. RBCs can be normochromic and normocytic with failure of erythroid production presenting as low reticulocyte count with nucleated RBC and tear drop forms[1].

Platelets may vary from normal count to extremely low count with normal size of the platelets. WBC-It can vary widely from having leucopenia to leukocytosis, 20% present with count of >50000 with absolute neutropenia, and peripheral blood showing blasts. Hyper eosinophilia can appear as presentation and disappears with induction, it is commonly associated with t(5,14) .10% of the ALL patients present with total count of >100000, which is termed as hyperleucocytosis. Hyperleucocytosis can lead to impedence in the microcirculation by intravascular clumping of poorly deformed blasts, leading to local hypoxemia, endothelial damage, hemorrhage and infarction. 2% of the ALL patients can have counts >200000. In Bone marrow we can see hypercellular and homogeneous population of cells (>50% of blasts in most cases)[1].

Diagnosis should be mainly established by cytomorphological examination of wright stained or May-Grunwald Giemsa smears of BM aspirate and /or peripheral blood. For the morphological classification FAB criteria and scoring system have been generally accepted .To differentiate from AML Sudan black (SB) or

myeloperoxidase (MPO) and non-specific esterase (NSE) are recommended. In case of ALL, the negative MPO reaction is seen and positive acid phosphatase reaction (not in all cases)[1].

Leukemia cells will have specific subsets of intracellular and surface molecules known as cluster of differentiation (CD) antigens, these are identified by flow cytometry and help in identifying the lineage and also for sub categorization. Diagnosis of leukemia is mainly by immunophenotyping which is based on fact that the cells in leukemia frequently have aberrant phenotypes compared to the normal cells ,they are known as leukemia associated phenotypes (LAP)[30].

Lineage	*Immunological subgroup*	*Frequency*	*Immunophenotypic profile*	*Remarks*
B-ALL	Early pre-B cell	60–70%	CD10, CD19, CyCD22, CD34, and Tdt positive. CD24 strongly positive, CD45 dim/-ve	Good except CD10-ve ALL, especially in <1 year age group, infantile leukemia associated with translocation of 11q23 and have poor prognosis
	Pre-B cell	20%	Cyu heavy chain, CD10, CD19, cyCD79a, and CD22 +ve	Poor compared to early pre-B. Expression of t(1:19) is the primary determinant of adverse prognosis in pre B-ALL
	Mature B-Cell	2–5%	Surface immunoglobulin (bright), CD19, CD20, CD22, CD24 +ve CD34. Tdt –ve.	Poor with standard ALL therapeutic regimen, but dose intensive chemotherapy leads to cure rate of 75%.
T-ALL	Pro-T-cell		CyCD3 and/or CD7 +ve	With more intensive chemotherapeutic approach outcome reaching to the level of non-T-cell ALL.
	Pre-T-cell		CyCD3, CD7, CD2 and/or CD5 +ve	
	Cortical T-cell		CyCD3, CD7, CD2 and/ or CD5 and CD1a +ve, co-expression of CD4/CD8	
	Mature T-cell		CyCD3, CD7, CD2 and/or CD5 and CD3 positive, segregated CD4 or CD8 +ve	

Table 1. Subtypes of Acute Lymphoblastic Leukemia

Cytogenetics are done in case ALL ,the blasts contain genetic abnormality that help to understand the pathogenesis and it strongly influence the prognosis, these are somatically acquired and include changes in the chromosome number (hypodiploid/

hyper diploid) and some chromosomal translocations. They can have high hyperdiploidy which is defined as around 51-65 chromosomes per cell or with a DNA index which is greater than 1.16, or hypodiploidy in which there will be less than 45 chromosomes. TEL-AML1 (t[12; 21]), MLL gene rearrangements ,E2A-PBX1(t[1; 19]) and Philadelphia chromosome (t[9; 22]) these are the chromosomal translocation seen in case of pre B ALL , TEL-AML1 is seen in 20-26% of the cases in developed countries and it is mainly found in younger children i.e between the age group of 2-9 years. Philadelphia chromosome is seen in 3% of the patients and is more common in older children with high WBC count. MLL gene rearrangement is seen in 5% of the ALL patients, t(4; 11) is most common one and these are the infants with high WBC counts and CNS disease. E2A- PBX1 is also seen in 5% of the ALL patients and these have higher risk of CNS relapse[30].

Trephine biopsy might be needed in some of the cases where the BM aspirate smears are acellular/ dry tap or in cases where blood transfusion/ treatment with steroids is there, it is recommended to obtain the biopsy in all the new cases of hematolymphoid malignancies and the material obtained can be used for immunophenotyping. It is important that renal function tests, liver function tests, serum LDH, serum electrolytes and serology are done routinely. There are indicators of Tumor burden like TLC, LDH levels and the extra-medullary involvement like hepatosplenomegaly and this will help us to find the patients who require urgent intervention[30] .CNS involvement in ALL is assessed by doing lumbar puncture, it is also done to give intrathecal chemotherapy[30].

Outcome of the ALL patients have improved over the years though the prognosis of the patients depends on many factors, still the type and response to treatment is the strongest one in predicting the outcome. Prognosis depends on host

biology, tumor biology (genotype of the leukemic cell) and response to the treatment. In the host biology we have two important factors that is age and gender. The age of the child at the time of diagnosis tells us about the expected clinical outcome. The prognosis is not so good in infants when compared to the patients who are between 1-10 years[30] . The better outcome in this age group is due to favorable cytogenetics on the blasts is seen in them like t(12; 21) and hyperdiploidy[30]. Infants have high risk of treatment failure as they usually present with high leukocyte count, have greater frequency of CNS involvement and very high incidence of having rearrangement in the MLL gene on chromosome 11 (80%). Patients who present with rearrangement in MLL and present at less than 6 months of age with very high leukocyte count (>300000) will have worst prognosis[30]. Adolescent have poor outcome than the children who are in the age group of 1-10years, due to high leukocyte count, high incidence of Philadelphia or Philadelphia like chromosome and they usually present with T cell type of immunophenotype[30]. These children also are found to have treatment related complications like pancreatitis, deep vein thrombosis, hyperglycemia and osteonecrosis which can have impact on the outcome[30].

As we know that ALL is more seen in males and along with it it is also found that the prognosis is better in females[30]. This could be due to testicular relapse seen in case of boys and also that they have increased risk CNS and BM relapse reason for which is not known. But with the current treatment regimens for ALL there is no much difference in the outcome among boys and girls[30].

Tumor biopsy also plays a very important role in prognostication which includes WBC counts, CNS involvement, testicular involvement, immunophenotype and cytogenetics, numerical and/or structural abnormalities of the chromosome, and early response to the treatment. Total leukocyte count of the patient (WBC count) tells

us about the tumor burden in the body. National cancer institute (NCI) has stratified patients with ALL in 2 subsets based on the total leukocyte count, if WBC count < 50,000 as standard risk and if WBC count > 50,000 as high risk. The unfavorable chromosomal abnormalities like t(9; 22) ,t (4; 11) and the T- cell immunophenotype were usually associated with high total leukocyte count[30]. Despite the intensified therapy for patients with CNS involvement, CNS positivity still remains to be a poor prognostic factor in patients of ALL. Based on the number of WBC and presence or absence of blasts in CSF, patients are divided into three groups.

CNS 1 : lymphoblasts are absent, CNS 2: less than 5 WBC per micro liter along with blasts and CNS 3: more than or equal to 5 WBCS per micro liter with presence of blasts or cranial nerve palsy. Intensified intrathecal therapy is given during induction phase to overcome the poor prognosis associated with CNS 2[30].Intensified therapy is also needed in traumatic LP in ALL patients as it increases the chances of CNS relapse in them[30].

Testes is involved in approximately 2% of the boys at the time of diagnosis and it is a poor prognostic factor but has lost the prognostic significance due to the aggressive treatment given so it is not considered as independent factor determining the prognosis of patient[30].

WHO classification of ALL as B lymphoblastic leukemia or T lineage lymphoblastic leukemia is based on the origin of cell which is identified mainly by cytoplasmic or surface expression of T cell or B cell antigens. The most common type that is precursor B cell ALL which is seen in 80-85% of the patients, is defined by the expression of cytoplasmic CD19, CD 79a, HLA- DR and some of the other B cell

antigens. Precursor B cell ALL is further immunological subtypes. In case of T ALL leukemia blast cells express cytoplasmic CD3, with CD7 and CD5 or CD2[30].

Early response to therapy tells us about the leukemic cells drug sensitivity, pharmacy genomics and the pharmacodynamics of the patient and also the intensity of the therapy, we assess it by seeing peripheral blood response after 7 days of steroid prophase, favorable prognosis is seen in patients if there is reduction in the peripheral blast count to < 1000/micro liter after the 7 days of induction with prednisone and intrathecal methotrexate , we also see day 7 and day 14 bone marrow responses[30].

After completing the induction phase we look for minimal residual disease, it detects malignant cells 1 in 1000 to 1 million cells. Patients who have higher level of end induction MRD (>0.01%) have poor prognosis than the patients with undetectable levels. Therefore post induction MRD plays a important role in determining the intensity of post induction treatment[30] .

The standard risk stratification for ALL is as per Children Oncology Group (COG) criteria adopted from National Cancer Institute (NCI)

Table 2 ALL risk stratification for treatment purpose.

B CELL ALL		
STANDARD RISK	**INTERMEDIATE RISK**	**HIGH RISK**
Age more than 1 year and less than 10 years Prednisolone good response No high risk cytogenetics WBC count <50,000/mm3 MRD <0.01% after induction Complete Remission after induction No CNS disease	Good risk features but age ≥10 years Good risk features but WBC ≥50,000/mm3 Good risk features but bulky lymph nodes (≥5 cm in peripheral region and in chest >5 cm on CT scan or occupying ≥1/3rd diameter on chest x-ray) and/or bulky liver/spleen reaching beyond umbilicus and/or presence of testicular disease MRD <0.01% after induction	All Prednisolone poor responsonders, irrespective of age and presenting WBC count High risk cytogenetics (Philadelphia chromosome positive or MLL rearranged) CNS disease MRD ≥0.01% after induction
T CELL ALL All T cell ALL were treated as high risk disease		

\TREATMENT OF ALL

Treatment of ALL consists of 5 phases and they are as follows:

Induction, Consolidation, Interim maintenance, Delayed intensification and maintenance phase. First phase also called as remission induction-it involves treatment for 4 weeks leading to eradication of all the cancer cells from the bone marrow. Second phase called as consolidation phase, aims on CNS therapy intensively along with systemic therapy intensively to prevent CNS relapse. Then we have intensification phase-first aggressive phase called as delayed intensification followed by it nontoxic interim maintenance phase. Finally patients will have maintenance phase which last for 2-3yrs[1].

Maintenance phase consists of 6MP which is given daily, MTX weekly and monthly pulses of dexamethasone and vincristine[47]

In Acute lymphoblastic leukemia series of trials were done which suggested long term remission was significantly improved when patients were started on maintenance therapy with two oral medications that is daily 6-MP and weekly MTX [48-52].The mechanism of action of 6-MP and MTX in maintenance therapy as antileukemic drug is poorly understood, but benefits with myelosuppressive therapy which is given for several years is well proven[53].Today ALL protocols include maintenance therapy with oral 6MP and MTX is given until 2-3yrs from diagnosis and longer duration is reserved for boys, due to inferior prognosis with shorter therapy[54-58].For some of the subsets of ALL including T-ALL and the ALL patients who present with hyper leukocytosis, adolescents and down syndrome maintenance therapy seems to be very important[59-62]

Observational studies have shown that 6MP/MTX is superior to other combination of drugs in maintenance phase chemotherapy[60] .It is also being proven, that there is significant increase in risk of relapse due to poor patient adherence and poor physician compliance[63-66].In 1960s importance of MTX/6MP dose was demonstrated first, where randomized children were receiving maintenance chemotherapy with vincristine,cyclophosphamide,6MP(50mg/m^2/d) and MTX(20mg/m^2/week)was having longer remission than other children who received half dose so as to reduce toxicity[67].

Because of large interindividual variations in cellular pharmacokinetics and bioavailability for the maintenance drugs i.e. 6MP/MTX there was difference in the systemic and intercellular drug exposures for patient with identical body surface area [68-74].The doses of 6MP and MTX are poorly relates to AUC[74] and the drug doses are not related significantly to relapse rates[75] .Accordingly, in ALL protocols 6MP and MTX recommended doses are regarded as a starting doses which are further adjusted individually based on myelotoxicity as per absolute neutrophil count[53].

Although after 28 days of induction phase 95% of the children undergo remission but 20% of children may relapse[7].Treatment of ALL requires a maintenance phase which is prolonged phase and where there is self or parent administration of oral antimetabolite chemotherapy which is given over 2years[8].Children with poor compliance in the maintenance phase have been found to have 3.9 fold increased risk of relapse, thus high lighting the importance of oral antimetabolite i.e 6-MP[7] .It is reported that patients with low erythrocyte levels of metabolites of 6-MP i.e 6-TGN are associated with relapse[53,76].Adherence rate for 6-MP less than 90% has increased risk of relapse[7].

This non adherence to the medication is found to be associated with an increase in mortality[7]. The outpatient treatment with oral 6MP is inexpensive and salvage treatment for relapse cases of ALL is very expensive and is also associated with morbidity and is unsuccessful This tells us the critical role of adherence and importance to develop measures to enhance the rate of adherence to the oral medication i.e 6MP[7]. Thus to monitor the adherence to 6MP it is important to know the metabolism of this drug.

6MP has rapid absorption and short half life i.e. 1to 2 hrs. Few studies have shown association between 6MP concentration in the plasma and relapse rates[77,78],but these levels could not be used for drug adjustment due to very large interindividual and intraindividual variation in the bioavailability[68,74,79].

There are 3 metabolic pathways of 6mp.

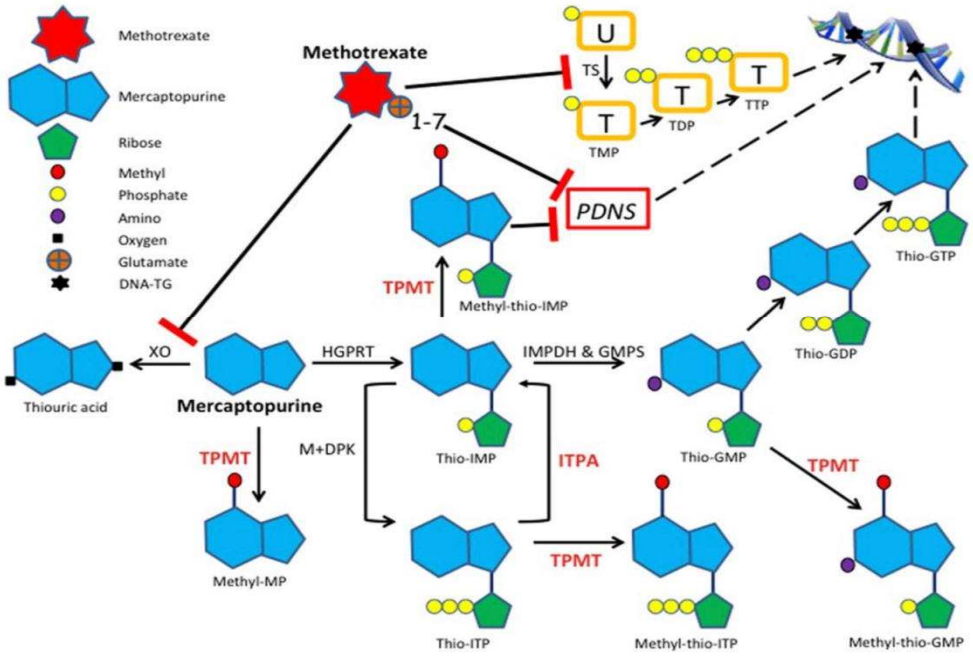


Figure 1. Metabolic Pathways of 6-Mercaptopurine

In the first pathway, 6MP is converted to 6thiouric acid which is the inactive form, via xanthine oxidase enzyme in first pass metabolism[68,69,80] . Allopurinol inhibits thiopurine methyl transferase and xanthine oxidase [81-83],and if allopurinol is administered with 6MP then it requires reduction of the dose, as this drug combination can lead to increased 6MP bioavailability and skews towards the production of 6TGN(6-thioguanine nucleotide)[84].

Second pathway is a multistep process, in which 6MP is prodrug leading to coupling with phosphoribosylpyrophosphate which is mediated by hypoxanthine guanine phosphoribosyltransferase, and there is base modification followed by phosphorylation, leading to formation of 6TGN. After that, the deoxy form of 6TGN is incorporated in nucleated cells, that is in the DNA(DNA-TG)[85-86].This DNA-TG leads to breaks in the DNA strands and then apoptosis via activating post replication mismatch repair systems[88-89].

In third pathway there is thiomethylation of 6MP and its metabolites and this leads to decreased 6TGN formation. This is catalyzed by TPMT[90].Earlier methylated 6mp metabolites had been considered insignificant in pharmacodynamics of 6MP.However some of the methylated metabolites act as strong inhibitors for de novo synthesis of purine[91].The salvage pathway for purine is low in lymphoblasts so they are mainly depend on de novo synthesis of purine[92],reduced endogenous nucleotide levels which resulted in enhanced DNA-TG incorporation in presence of the MeMP plays a clinical role[87,93].Impact of these interactions on toxicities and relapse rates still remains undetermined, partly due to recent availability of sufficiently sensitive and reliable assay of DNA-TG in nucleated blood for routine measurements[94].

Toxicities associated with 6MP administration are as follows

1)Leukopenia-Drug adjustments of 6MP is mainly guided by the toxicity caused by it assuming the individual variation of pharmacokinetics and pharmacodynamics of the drug will affect both leukemic and normal cell parallely[95].During maintenance phase the studies have showed that low ANC and/or low WBC is related to RBC cytotoxicity and reduced relapse rate[65,75,96,97].

2) Thrombocytopenia- Thrombocyte count in maintenance phase during the phase and after cessation are correlated significantly[98], but rarely it is dose limiting factor. If patients on 6MPhave unexplained thrombocytopenia, they should be checked for persistent parvovirus B19 infection and hypersplenism[99].

3) Hepatotoxicity-Both 6MP as well as MTX are hepatotoxic and frequently 2 fold increase or more of aminotransferases is seen[97].They usually normalize in few weeks after discontinuation of drugs[100,101]. Hypoglycemic episodes while fasting[102-105] is associated with high levels of methylated 6MP metabolities[106].Some patients develop hypoglycemic symptoms like severe nausea, itching or malaise which might require dose reduction. Moderate rise in level of bilirubin or decrease in coagulation factor level may be seen, but risk of permanent liver damage is low[107-109].

The cornerstone for maintenance therapy i.e 6MP is a cytotoxic drug and is associated with hematologic and hepatic toxicities , thus requiring dose modifications and interruptions. Germ-line genetic-variations mainly determine interindividual variability in terms of drug tolerance, dosage and side effects[110].

It is found that polymorphisms in enzymes which are involved in metabolism of 6MP, namely NUDT 15, ITPA and TPMT are associated with decreased tolerance. These polymorphisms have varied prevalence across the population of different ethnic group across the world[110].Till date, TPMT is maximum studied polymorphism which

is involved in metabolism of 6MP. Incidence of TPMT polymorphism is 10-15%.The most commonly seen polymorphism is TPMT*3A in Caucasian people . In southeast Asia, it accounts for only 5% (TPMT*3C is common)and in India, the prevalence for TPMT is less than 5% is the [110],thus tells us that in this region it does not play any role in toxicity[110]

Polymorphism of ITPA is found to be prominent in south east asia based on reports. ITPA94CA and 198CA are relevant and maximum studied polymorphism and it is seen in 20-40% of patients in South East Asia. Among the Indian origin 11-22% have the polymorphism. Whereas the prevalence of this polymorphism is very less in European and south American population it is barely 2% and 3-5% respectively[110].

NUDT15 polymorphism is found to be associated with intolerance to 6MP. Incidence is varied i.e Thia (15%), Korea(23%), Europe(<1%) and in south east asia(9.5%). There are some studies showing conclusive evidence regarding the relationship between dose of the drug i.e 6MP and the toxicity in patients who have NUDT15 polymorphism in Asian population[110] and they lower cumulative dose.

In patients of maintenance phase chemotherapy our goal is to get a required levels of ery-6TGN as they are related to DNA TG levels and the steady state level of ery-6TGN level is being obtained after taking oral 6MP for few weeks[111,112].Earlier studies have showed association of remission and myelotoxicity with Ery-6TGN[113-115],though 6MP metabolite profile differ between both neutrophils and RBC[116].Ery-6TGN levels shows adherence to 6MP[117] and TPMT activity[118], they are weakly but statistically significantly related to the DNA TG levels[87,93].By increasing 6MP dose to get higher levels of ery-6TGN ,which also lead to increase in the methylated metabolite levels[119] enhancing hepatotoxicity[120]

Several studies have showed that there is decreased bioavailability of 6MP and MTX when administered with food[70], and especially when 6MP is administered with milk because it contains xanthine oxidase[121].

In Pediatric patients poor adherence to the medication is seen, rate of non adherence range from 25% to 60%[122-125].Patients with ALL once they attain remission they become asymptomatic ,they still require a complex treatment, so it is expected that the patients will not be adherent[126].17-46% of ALL cases in adolescents and children have been reported with non adherence to 6MP[127].Due to the poor adherence there are many consequences like course of illness is extended, symptoms are poorly controlled, repeated clinic visits and increased cost due to requiring hospital admissions[128].So non adherence is of concern significantly in chronic illness.

In Children with ALL adherence to chemotherapy mainly oral is a multidimensional and complex behavior that is predicated on understanding of the parent and children and carrying out the complex instructions which are given by the health provider about the medications ,some of them with parameters associated with the medications regarding time of administering the medication and administering it with or without food or dairy products, and all of them which will require frequent dose adjustments in response to infections, blood counts, change in the weight/BSA and clinical course[8]. Therefore adherence also requires the cognitive capacity along with psychomotor skills to carry out the process along with the willingness to stick to a prescribed regimen for a prolonged period[8].

There are many cultural and socioeconomic issues that might affect the patient and the ability of the family to adhere to the medication regimen which is prescribed like language and financial barriers and difficulty accessing the medical care[8].

In Childhood ALL there is an important role of clearly identifying a person who is responsible in ensuring that the oral chemotherapy is administered at home in the prescribed doses and on daily basis[8].

In childhood ALL adherence to the chemotherapy in maintenance phase can be measured indirectly and directly. Direct method of measuring adherence –by doing red blood cell assays of 6MP metabolites,that is thioguanine nucleotide,6-methylthioinosine monophosphate and methylated mercaptopurine (Dervieux et al., 2002; Lennard et al., 1990; Lennard & Singleton, 1992) via different pathways and will have different concentration patterns in nonadherent and adherent patients (Lennard et al., 1995)[8].

Surrogate measures have also being used to assess adherence in children with ALL which include White blood count or neutrophil count (de Oliveira et al., 2004),and behavioural observations lik electronic medication monitoring device and pillcounts(Lau et al., 1998; Pritchard, Butow, Stevens, & Duley, 2006).Indirect methods include the selfreport by the patient and/or parent via interviews, diaries and questionnaires(Davies, Lennard, & Lilleyman, 1993; Pritchard et al., 2006; Tebbi et al., 1986)[8].

Due to the fact that chemotherapy regimen in ALL involves administering multiple agents on different schedules with different parameters (Landier, 2001; Pui & Evans, 1998), and requiring frequent dose adjustments(Davies & Lilleyman, 1995) makes the adherence to chemotherapy challenging[8].Non adherence to oral 6MP in children with ALL has been seen in 10%(Lennard et al., 1995) to more than 50%(de Oliveira et al., 2004; Festa, Tamaroff, Chasalow, & Lanzkowsky, 1992)[8].

Clinical implications for healthcare providers include recognition of the importance of clear communication of instructions and reinforcement of adherence-related behaviors in children and adolescents with ALL and their families. The multifaceted nature of adherence in this population may present challenges to healthcare providers, who must assess child and parental capacity for adherence, address knowledge deficits, and assist with common issues related to daily medication administration, such as pill-swallowing skills and reminder systems.

One of the study done by Children's Oncology group on African Americans, Asian Americans and non-Hispanic whites it showed that there was high adherence seen in the non-Hispanic whites(as high as 95%) ,the children of the mothers who are educated and staying in nuclear family. It was also found that reasons for missing 6MP were forgetfulness, refusal to take, and some logical barriers[7] .

A disease management plan that addresses the specific needs of individual children and adolescents and their families may be helpful in promoting adherence in this population. Several gaps exist in the literature regarding adherence to oral chemotherapy in childhood ALL. Investigations are needed to determine the complexity of health behaviors required to be fully adherent with the prescribed maintenance chemotherapy regimen and the role of healthcare providers in fostering adherence in this population. In addition, the barriers and facilitators to adherence as perceived by children and adolescents with ALL and their parents or caregivers need to be identified. These data are critical to inform development of interventions aimed at improving adherence to oral chemotherapy, an area ripe for future research.

As there are very less studies mainly in the Indian setting to tell us the adherence of the patient and there is need for simple intervention mainly in LMIC to

increase the adherence and to overcome some of the barriers of non adherence, we are bringing a intervention that is we are providing a smart pill box to the patient which consists of alarm so as to remind them every day at the same time to take the medication and thus to increase the adherence to prevent the relapse in patients with acute lymphoblastic leukemia.

MATERIAL AND METHODS

STUDY DESIGN: Prospective Interventional study.

STUDY SETTING: This study was conducted in the Paediatric Oncology OPD of a tertiary care hospital

PARTICIPANTS

40 newly diagnosed cases of ALL between 0 to 18 years of age, who had completed at least one month of maintenance chemotherapy between November 2020 to December 2021 were enrolled in the study. Eligible candidates were included in the study after taking informed consent in their vernacular language. Clinical, demographic and laboratory data (CBC, LFT) of recruited children were noted and TPMT and NUDT mutation analysis was done.

Adherence was assessed first by the subjective method by Kannada, Marathi, Hindi and English translated and validated version of Morisky Medication Adherence Scale (MMAS-8)[129]. Parents of subjects were interviewed as per the questionnaire in MMAS-8. If the age of the child was more than 10 years then the child was also subjected to MMAS-8. Response choices in morisky scale were “yes” or “no” for items 1 through 7 and Item 8 had a five-point Likert response scale. Each “no” response was rated as 1 and each “yes” response was rated as 0 except for item 5, in which each “yes” response was rated as 1 and each “no” response was rated as 0. For Item 8, the code (0-4) had to be standardized by dividing the result by 4 to calculate a summated score. The total scores on the MMAS-8 range was 0 to 8, with scores of >7.2 reflecting high adherence, 7.2 or 6 reflecting medium adherence, and <6 reflecting low adherence.

4ml whole blood was collected from each patient and 6-MP metabolites (6 -TGN and 6-Mmp) in RBCs were measured by a validated method. Cryopreserved Packed RBCs were suspended in 500ul in PBS, and 250 mL of the solution was dispensed into a 1.5ml Microfuge tube. The hydrolysis and extraction process were performed as follows: diluted RBC solution (250 uL) was mixed with 20ul of IS, 20ul of 1.1 M dithiothreitol, and 50ul of DW, vortexed for 30 seconds, and spun down. Then, 34 mL of 70% perchloric acid was added, vortexed for 30 seconds, and centrifuged at 3000g for 15 minutes at room temperature. The supernatant (220 ul) 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 220ul of sodium hydroxide. Then, 50ul of this solution was transferred to 1.5ml of Microfuge tube and dried using Speed Vacuum, (Thermofisher Scientific,Cat.No. SPD1030-230) at low energy for 30-35 Minutes. Samples pellets were then re-suspended using 50ul methanol: water (1:1, water: methanol) mixture for injection. Or the samples can be stored at -20°C without re-suspending it. UHPLC-MS(MS) analysis was performed using a Dionex Ultimate 3000 UHPLC 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 MS Tune 2.8 SP1 (Thermo Fisher Scientific, Breda, The Netherlands).

Figure 2. Q Exactive mass spectrometer

Then Calculating amounts of 6TG and 6MMP in the samples on the basis of comparison of peak intensities with that of the internal standards. Cluster analysis of 6TG and 6MMP levels were used to define whether a patient is adherent or not.

INTERVENTION

Parents and older children (>10yrs) were educated and they were provided Istore medicine storage box (smart pill box) with inbuilt alarm. 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 a reminder for the patient to take the medication at the scheduled time. To reinforce this, an alarm was

also set for the same time in the caregiver's mobile. After 2 months of intervention, children were assessed again for adherence by above described 2 methods.

Figure 3. Smart pill box

SAMPLE SIZE

A total of 40 patients were enrolled

STATISTICAL ANALYSIS

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Non normally distributed quantitative variables were summarized by median and interquartile range (IQR). Data was also represented using appropriate diagrams like bar diagram, pie diagram and box plots. All Quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro- wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was

considered as normal distribution. Categorical outcomes were compared between study groups using Chi square test /Fisher's Exact test (If the overall sample size was < 20 or if the expected number in any one of the cells is < 5, Fisher's exact test was used.) Categorical variables at different time periods of follow-up 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 (2 groups) The change in the quantitative parameters, before and after the intervention was assessed by paired t-test (In case of two time periods). For normally distributed Quantitative parameters the mean values were compared between study groups using ANOVA (>2 groups). For non-normally distributed Quantitative parameters, Medians, and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). The change in the quantitative parameters, before and after the intervention was assessed by Wilcoxon signed-rank test (In case of two time periods). For non-normally distributed Quantitative parameters, Medians, and Interquartile range (IQR) were compared between study groups using Kruskal Wallis test (> 2 groups). Association between quantitative explanatory and outcome variables was assessed by calculating Pearson correlation coefficient and spearman correlation and the data was represented in a scatter diagram. Linear regression was performed to assess the outcome parameter using the explanatory variables by forming the linear regression equation.

Two numerical parameters (6TG & 6 MMP levels) were used perform cluster analysis hierarchical agglomerative method used to perform cluster analysis Clustering is a broad set of techniques for finding subgroups of observations within a data set. Clusters 1 were characterized by very low levels (i.e. above 20th percentile cutoff point) of 6-TGN levels and 6-mMP levels, these were considered to be non

adherent and other 3 clusters were considered adherent. P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis. After 2 months, children were assessed for impact of intervention on adherence by repeating 6-MP metabolite levels and subjecting the caregiver and children (>10yrs) again to MMAS. The mean score of MMAS were calculated and the pre and post intervention mean scores were compared by using chi square test. The hierarchical cluster analyses of drug metabolite concentrations were done and the pre and post intervention levels were compared.

RESULTS

Over a year, a total 40 patients between the age of 0-18yrs who were diagnosed with Acute Lymphoblastic Leukemia and had completed 1 month of maintenance phase of chemotherapy were taken in the study, to look for the compliance and also see for the improvement in the compliance after intervention with smart pill box and parent intervention.

Demographic and Clinical characteristics of ALL cases

Table 3: Descriptive analysis of Demographic Parameters in the study population (N=40)

Demographic Parameters	Mean ± S.D	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Age	7.39±4.29	6.25	1.50	17.00	6.06	8.71
Distance from KLE hospital (kg)	91.76±62.69	100.00	3.00	220.00	71.83	111.70
Weight	21.48±12.54	16.95	8.30	16.95	17.59	25.37
Height	110.23±25.57	106.50	44.00	175.00	102.30	118.15
BMI	17.35±8.63	15.27	10.75	67.15	14.68	20.03
BSA	0.80±0.30	0.72	0.42	1.60	0.70	0.89
Gender	**Frequency**	**Percentages**				
Male	24	60.00%				
Female	16	40.00%				

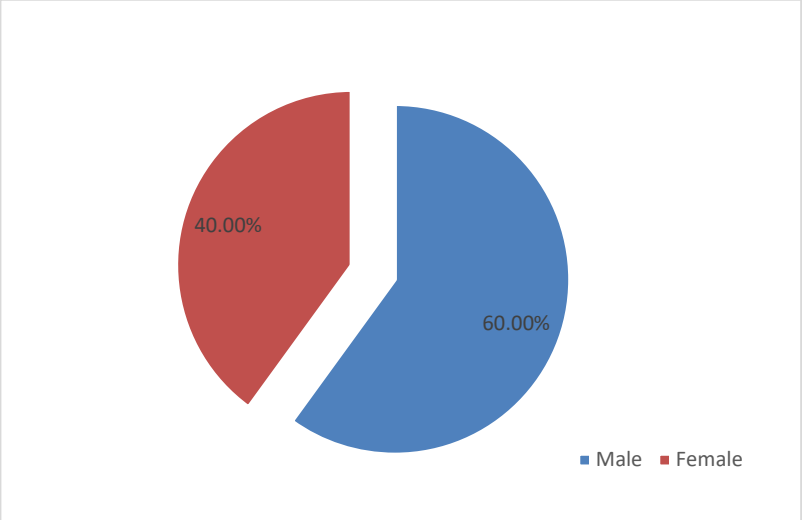


Figure 4: Pie Chart of Gender

Among the 40 patients in the study mean age was 7.39±4.29, lowest age being 1.5yrs and oldest patient was 17year old. 60% of the patients were male, with male: female ratio of 1.5:1. Patients were even from 220km from the hospital, mean distance of 91.76±62.69 km was seen.

Table 4: Descriptive analysis of Diagnosis in the study population (N=40)

Diagnosis	Frequency	Percentage
B-All	35	87.50%
T-All	5	12.50%

Table 5: Descriptive analysis of Risk stratification in the study population (N=40)

Risk stratification	Frequency	Percentage
Intermediate	31	77.50%
High	9	22.50%

Table 6: Descriptive analysis of Current number of maintenance cycle in the study population (N=40)

Current number of maintenance cycle	Frequency	Percentage
M1	13	32.50%
M2	8	20.00%
M3	2	5.00%
M4	4	10.00%
M5	6	15.00%
M6	3	7.50%
M7	3	7.50%
M8	1	2.50%

As per immunophenotype, B ALL was the most common type of ALL accounting to around 87.50%, based on the various factors and the type of ALL for the treatment, risk stratification was done. Maximum of them belonged to Intermediate risk i.e 77.50% and 22.50% belonged to high risk. Maintenance phase of chemotherapy for ALL which lasts for 2yrs , most of our patients belonged to M1 cycle.

Table 7: Descriptive analysis of Post induction MRD status in the study population (N=40)

Post induction MRD status	Frequency	Percentage
Positive	2	5.00%
Negative	38	95.00%

MRD was estimated by flow cytometry at the end of induction, and those who had MRD < 0.01% were considered MRD negative. Minimal Residual Disease is important indicator of the effectiveness of the treatment. 2 of our patients had MRD positive i.e 5% of the patients.

Table 8: Descriptive analysis of TPMT mutation status in the study population (N=40)

TPMT mutation status	Frequency	Percentage
Negative	40	100.00%

Table 9: Descriptive analysis of NUDT mutation in the study population (N=39)

NUDT mutation	Frequency	Percentage
Positive	4	10.26%
Negative	35	89.74%

Table 10: Descriptive analysis of Doses in the study population (N=40)

Doses	Mean ± S.D	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Dose of 6mp BSA	47.73±18.20	42.90	25.20	96.00	42.08	53.37
Dose of 6mp total	44.36±14.02	41.56	21.60	78.20	40.01	48.70
Dose of methotrexate BSA	15.91±6.07	14.30	8.40	32.00	14.02	17.79
Dose of methotrexate total	23.63±6.98	20.00	15.00	45.00	21.46	25.79

Maintenance phase of chemotherapy of ALL mainly consists of two oral drugs i.e 6-Mercaptopurine and Methotrexate. These drugs are metabolized by enzymatic reaction, so the mutation of TPMT and NUDT play role to determine there dose. All of our patients tested negative for TPMT mutation whereas 10.26% of them were positive for NUDT mutation. Dose of these medications is mainly calculated by BSA of the child and further modified based on the blood reports.

Table 11: Descriptive analysis of Morisky scale baseline in the study population (N=40)

Morisky scale	Frequency	Percentage
Morisky scale(parent) baseline		
High adherence	20	50.00%
Medium adherence	17	42.50%
Low adherence	3	7.50%
Morisky score of patients (>10yrs) baseline		
High adherence	3	23.08%
Medium adherence	10	76.92%

Figure 5: Pie Chart of Morisky scale(parent) baseline

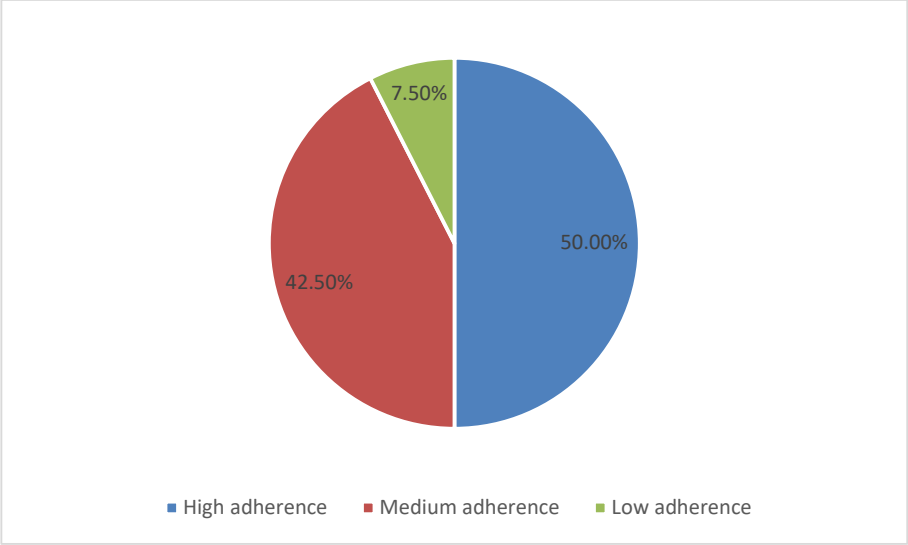


Figure 6: Pie Chart of Morisky score of patient (>10yrs) baseline

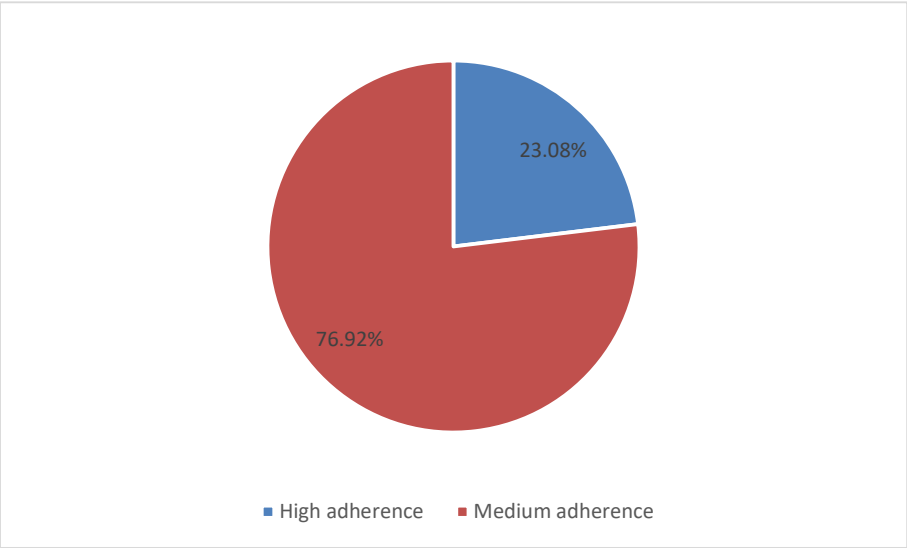


Table 12: Cluster Distribution of subjects for 6 MMP & 6 TGN Baseline levels

Clusters	Frequency	Percentages
Cluster 1 : Very Low 6 MMP & Very Low 6 TGN	4	10.00%
Cluster 2 : Low 6 MMP & Low 6 TGN	30	75.00%
Cluster 3 : Medium 6 MMP & Low 6 TGN	4	10.00%
Cluster 4 : Low 6 MMP & High 6 TGN	2	5.00%

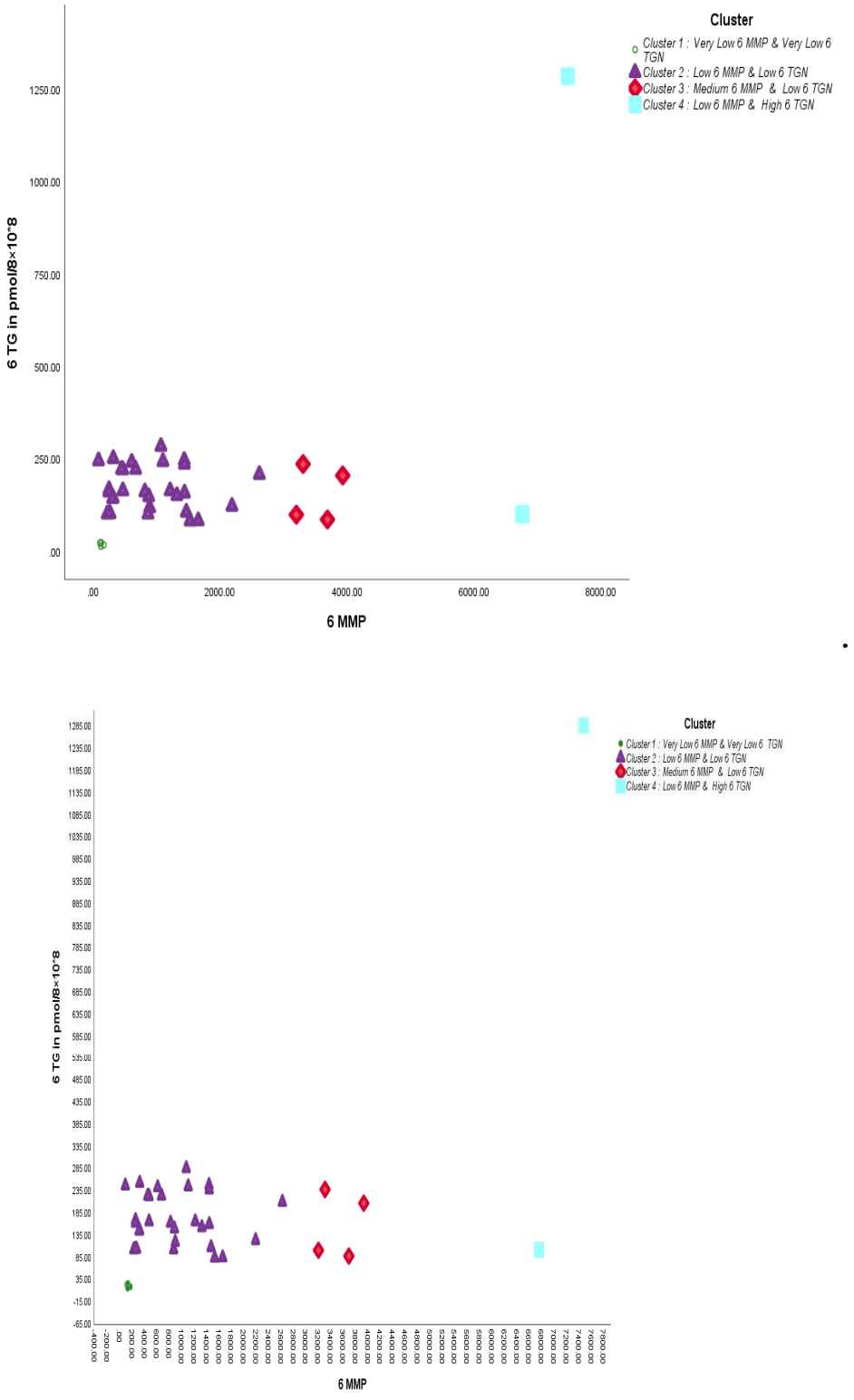
75% of the patients were in cluster 2 i.e with low 6 MMP and low 6 TGN.

Table 13: Median & IQR cluster wise for 6 MMP & 6 TGN Baseline levels.

Clusters	Median (IQR)	
	6 TG in pmol/8×10*8 (Baseline)	6 MMP (Baseline)
Cluster 1 : Very Low 6 MMP & Very Low 6 TGN	18.5 (13.75,22.5)	127.5 (113.75,160)
Cluster 2 : Low 6 MMP & Low 6 TGN	160 (114,224.5)	842 (316.75,1437.75)
Cluster 3 : Medium 6 MMP & Low 6 TGN	151 (88.25,227.25)	3499 (3227.5,3871)
Cluster 4 : Low 6 MMP & High 6 TGN	691.5 (395.2, 987.8)	7116 (6396,7229)

Median level of 6TGN in the cluster 2 was 160 pmol/8×10*8

Figure 7,8: Scatter plot showing the clusters for 6 MMP & 6 TGN Baseline levels



Compliance of the patient to these medications play a important role in the treatment of ALL, it can be measured by a subjective method i.e by using questionnaire Morisky medication adherence scale. In our study we found that based on the answers given by the parents 50% of the patients had high adherence, 42.5% had medium adherence and 7.5% had low adherence. Based on the answers given by the patients who were >10yrs of age 23.08% of patients had high adherence, whereas 76.2% belonged to medium adherence category.

Objective method to look for the compliance of the patients to 6-MP was done by measuring the metabolite levels i.e 6 TG levels in the RBC's, it was found that the mean level of 6TG was 215.91±240.20, with minimum level among the patients being 81.40 pmol/8×10*8 and maximum being 1284 pmol/8×10*8

Table 14: Descriptive analysis of Parameters in the study population (N=40)

Parameters	Mean ± S.D	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Baseline						
6 TG in pmol/8×10*8	215.91±240.20	160.00	81.40	1,284.00	141.47	290.35
6 MMP	1,553.55±1,669.37	1,038.00	88.00	7,474.00	1,036.21	2,070.89

Table 15: Comparison between with Parameter Morisky scale(parent) baseline (N=40) [One-way ANOVA]

Parameter	Morisky scale(parent) baseline			P Value
	High adherence (N=20)	Medium adherence (N=17)	Low adherence (N=3)	
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	8.25 ± 4.49	6.79 ± 4.25	5.00 ± 2.00	0.3646 ¥
Distance from KLE hospital (kg)	86.90 ± 64.72	92.60 ± 66.31	120.00 ± 26.46	0.7050 ¥
Dose of 6mp total	46.14 ± 15.05	42.69 ± 14.10	41.93 ± 5.25	0.7321 ¥
Dose of methotrexate total	25.00 ± 7.78	22.35 ± 6.40	21.67 ± 2.89	0.4659 ¥
ANC	1890.00 ± 571.15	1911.76 ± 1214.95	1666.67 ± 850.49	0.9123 ¥
Age (Mother)	31.85 ± 4.53	29.71 ± 5.59	28.00 ± 4.00	0.2835 ¥
Age (Father)	37.25 ± 4.97	37.19 ± 7.27	35.67 ± 4.04	0.9108 ¥

¥-ANOVA P-value

Table 16: Comparison between Total number of family members with Morisky scale(parent) baseline (N=40) [Kruskal Wallis one-way analysis of variance]

Parameter	Total number of family members	Kruskal Wallis Test (P Value)
	Median (IQR)	
High adherence (N=20)	6.00(5.0 to 9.0)	0.1030 €
Medium adherence (N=17)	5.00(4.0 to 6.0)	
Low adherence (N=3)	6.00(5.5 to 8.5)	

€- Kruskal Wallis Test (P Value)

Table 17: Comparison Between Gender, Risk stratification, Number of siblings & Socio-economic status , Type of family , Education (Mother) & Education (Father) with Morisky scale(parent) baseline in the study population (N=40)

Parameter	Morisky scale(parent) 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%)		
Risk stratification					
Intermediate	14 (70.00%)	14 (82.35%)	3 (100.00%)	-	*
High	6 (30.00%)	3 (17.65%)	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%)		
Socio economic status					
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%)		

Parameter	Morisky scale(parent) baseline			Chi square value	P value
	High adherence (N=20)	Medium adherence (N=17)	Low adherence (N=3)		
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%)		
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%)		

***-No Test is Applicable due to the nature of the data**

Table 18: **Comparison between Age, Distance from kle hospital (kg), Dose of 6mp total, Dose of methotrexate total, ANC, Age (Mother) & Age (Father) with Morisky score of patients (>10yrs) baseline in the study population**

Parameter	Morisky score of patients (>10yrs) baseline		P Value
	High adherence (N=3)	Medium adherence (N=10)	
	Mean ± SD	Mean ± SD	
Age	12.67 ± 2.08	12.90 ± 2.23	0.8753 £
Distance from KLE hospital (kg)	101.33 ± 98.01	75.50 ± 55.00	0.5581 £
Dose of 6mp total	54.40 ± 21.81	60.32 ± 12.03	0.5425 £
Dose of methotrexate total	33.33 ± 2.89	30.00 ± 7.82	0.4952 £
ANC	1766.67 ± 450.92	1910.00 ± 962.00	0.8115 £
Age (Mother)	34.33 ± 8.02	34.60 ± 4.74	0.9425 £
Age (Father)	40.00 ± 11.14	41.10 ± 6.81	0.8338 £

£-IST P-value

Table 19: Comparison Between Total number of family members with Morisky score of patients (>10yrs) baseline (N=13) [Mann Whitney U Test]

Parameter	Total number of family members	Mann Whitney U Test (P Value)
	Median (IQR)	
High adherence (N=3)	5.00(5.0 to 15.0)	0.3330 ®
Medium adherence (N=10)	5.50(4.25 to 6.0)	

Table 20: Comparison Between Gender, Risk stratification, Number of siblings & Socio-economic status, Type of family, Education (Mother) & Education (Father) with Morisky score of patients (>10yrs) baseline in the study population (N=40)

Parameter	Morisky score of patients (>10yrs) baseline		Chi square value	P value
	High adherence (N=3)	Medium adherence (N=10)		
Gender				
Male	2 (66.67%)	5 (50.00%)	0.26	1.0000
Female	1 (33.33%)	5 (50.00%)		
Risk stratification				
Intermediate	3 (100.00%)	5 (50.00%)	-	*
High	0 (0.00%)	5 (50.00%)		
Number of siblings				
One	0 (0.00%)	6 (60.00%)	-	*
Two	2 (66.67%)	2 (20.00%)		

Parameter	Morisky score of patients (>10yrs) baseline		Chi square value	P value
	High adherence (N=3)	Medium adherence (N=10)		
Three	1 (33.33%)	2 (20.00%)		
Socio economic status				
II	0 (0.00%)	1 (10.00%)	-	*
III	0 (0.00%)	2 (20.00%)		
IV	1 (33.33%)	4 (40.00%)		
V	2 (66.67%)	3 (30.00%)		
Type of family				
Joint	1 (33.33%)	3 (30.00%)	0.01	1.0000
Nuclear	2 (66.67%)	7 (70.00%)		
Education (Mother				
No formal education	0 (0.00%)	2 (20.00%)	-	*
Primary education	1 (33.33%)	3 (30.00%)		
Secondary education	2 (66.67%)	5 (50.00%)		
Education (Father)				
No formal education	1 (33.33%)	1 (10.00%)	-	*
Primary education	0 (0.00%)	3 (30.00%)		
Secondary education	2 (66.67%)	4 (40.00%)		
Graduate	0 (0.00%)	2 (20.00%)		

***-Chi-sq.** **P-value**

Various factors that affects compliance (based on MMAS) were taken into consideration as listed above, none of them were found statistically significant.

Table 21: Descriptive analysis of Morisky scale follow up in the study population (N=40)

Morisky scale	Frequency	Percentage
Morisky scale (Patients) follow up		
High adherence	26	65.00%
Medium adherence	14	35.00%
Morisky score of patients (>10yrs) baseline follow up		
High adherence	10	76.92%
Medium adherence	3	23.08%

Figure 9: Pie Chart of Morisky scale(parent) follow up

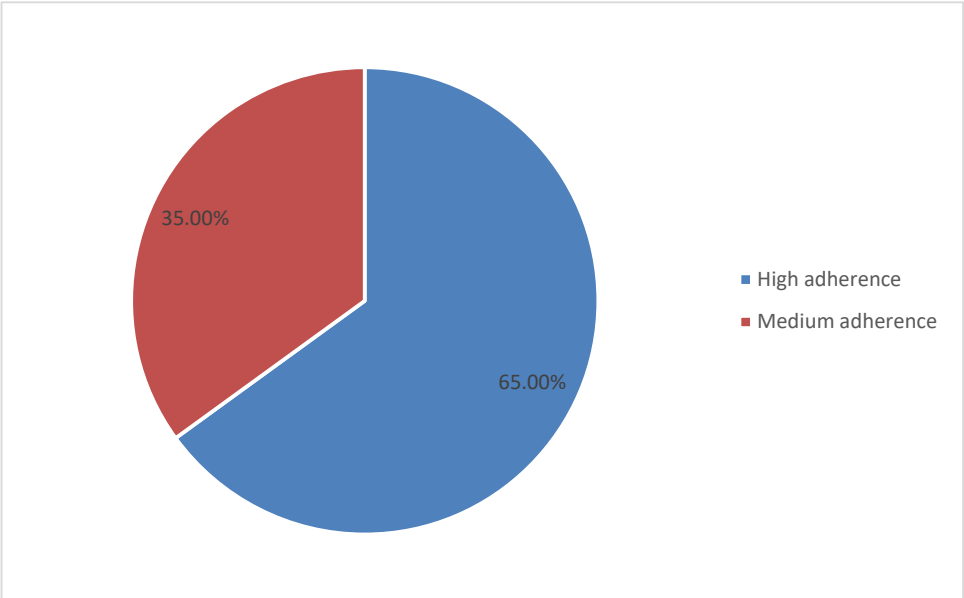


Figure 10: Pie Chart of Morisky score of patients (>10yrs) baseline follow up

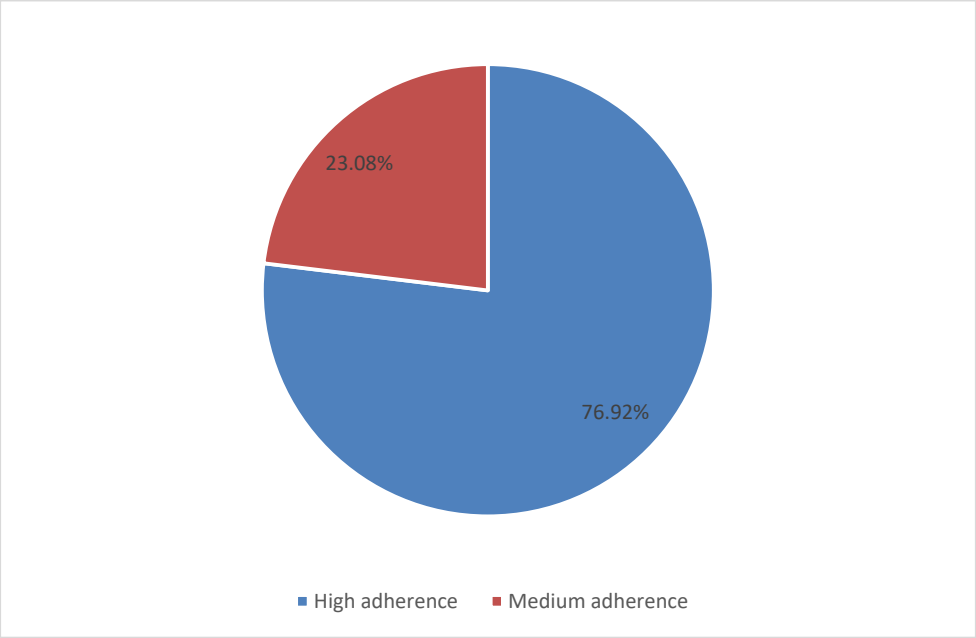


Table 22: Descriptive analysis of Objective Parameters in the study population at follow up (N=40)

Parameters	Mean ± S.D	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Follow-up						
6 TG in pmol/8×10*8	265.10±91.00	252.00	147.00	546.00	236.90	293.30
6 MMP	2,637.65±4,428.67	1,646.50	217.00	28,738.00	1,265.19	4,010.11

Along with a small intervention with a smart pill box and parent education so as to improve the compliance, we found that based on scoring done by the parents, there was improvement in the adherence score i.e from 50% of them belonging to high adherence to 65%. Based on the scoring given by the patients themselves scores improved from 23.08% to 76% in the high adherence category. Hence when the Morisky scale for adherence were compared between the baseline and on follow up the improvement was found with the p valve of 0.015 for parent score and 0.040 for patients score.

There was improvement in the mean 6TG levels, it was 265.10±91.00 pmol/8×10*8. On the follow up the minimum level was 147 pmol/8×10*8 and maximum was 546 pmol/8×10*8.

Along with 6TG the other metabolite 6MMP is also produced, mean 6MMP levels were 1,553.55±1,669.37 pmol/8×10*8 and after 2 months at follow up mean levels were 2,637.65±4,428.67 pmol/8×10*8.

Table 23: Cluster Distribution of subjects for 6 MMP & 6 TGN Follow up levels

Clusters	Frequency	Percentages
Cluster 1: Low 6 MMP & 6 Medium TGN	37	92.50%
Custer 2: High TGN	1	2.50%
Custer 3: Low 6 MMP & 6 High TGN	2	5.00%

After 2 months of follow up 92.50% patients were in the low 6MMP and Medium 6TGN suggests that there was improvement in the compliance.

Table 24: Median & IQR cluster wise for 6 MMP & 6 TGN Follow up levels.

Clusters	Median (IQR)	
	6 TG in pmol/8×10*8 (Follow-up)	**6 TG in pmol/8×10*8 ((Follow-up)**
Cluster 1: Low 6 MMP & 6 Medium TGN	245 (196.5,307)	1615 (875,3483)
Custer 2: High TGN	546 (546,546)	28738 (28738,28738)
Custer 3: Low 6 MMP & 6 High TGN	482 (468.5, 495.5)	1344 (1005,1682)

Median level in that criteria was 245 pmol/8×10*8.

Figure 11: Scatter plot showing the clusters for 6 MMP & 6 TGN Follow levels.

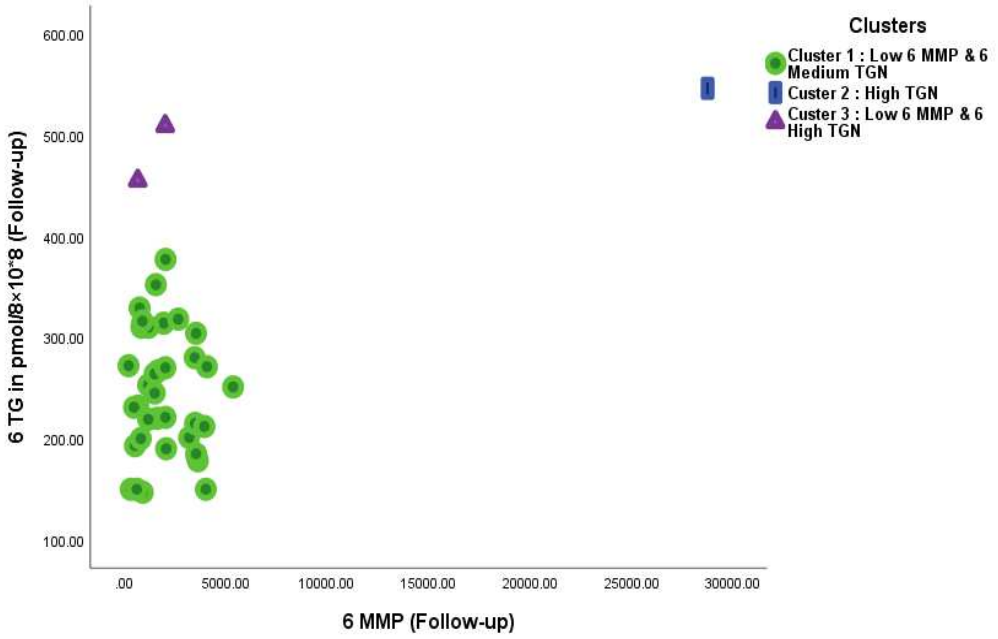


Table :25 6 MMP (Baseline) with SGOT (N=40) [correlation table]

Parameter	6 MMP (Baseline)	P Value
	r Value	
SGOT	-0.05	0.7734
SGPT	0.01	0.9735

Correlation between the 6MMP levels and the SGOT, SGPT levels was done and the p value was not statistically significant.

Table 26: **Comparison of Morisky score, 6TGN 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		
Morisky Scale Patients Score (N=13)			
Baseline	7.40 ± 0.58	-0.37	0.040
Follow-Up	7.77± 0.53		
6 TGN in pmol/8X10^8 RBC	**Median (IQR)**	**Wilcoxon's sign rank test statistics**	**P Value**
Baseline	150 (100,221)	-4.80	<0.001
Follow-Up	253 (200,314)		
6 MMP in pmol/8X10^8 RBC			
Baseline	879 (270,1528)	-3.82	<0.001
Follow-Up	1678 (900,3493)		

Baseline median values of 6TG when compared with the follow up values, there was improvement in the levels and it was statistically significant with p value <0.001. There was an increase 6 MMP level between the baseline and follow up it was also statistically significant.

Table 27: **Correlation Between 6 TG in pmol & Morisky Score between (N=40)**

Parameter	6 TG in pmol (Pre)	P Value
	r Value	
Morisky Scale Parent Vs 6 TG in pmol		
Baseline	-0.2732	0.3632
Follow-Up	-0.2185	0.4304
Morisky Scale Patients Vs 6 TG in pmol		
Baseline	0.0458	0.6484
Follow-Up	0.0796	0.3674

Table 28: Morisky scale(parent) follow up * Morisky scale(parent) baseline Crosstabulation

Parameter	Morisky scale(parent) baseline			McNamar-Test	P value
	High adherence	Low adherence	Medium adherence		
High adherence	15 (75.00%)	2 (66.7%)	9 (52.9%)	4.14	0.2464
Low adherence	0 (0%)	0 (0%)	0 (0%)		
Medium adherence	5 (25.00%)	1 (33.3%)	8 (47.1%)		

Table 29: Morisky score of patients (>10yrs) baseline follow up with Morisky score of patients (>10yrs) baseline

Morisky score of patients (>10yrs) baseline follow up	Morisky score of patients (>10yrs) baseline		McNamar-Test	P value
	High adherence	Medium adherence		
High adherence	2 (66.7%)	8 (80.00%)	5.44	0.046
Medium adherence	1 (33.3%)	2 (20.00%)		

DISCUSSION

Maintenance phase chemotherapy is an integral and very important part of treatment of children with ALL. During maintenance phase chemotherapy for ALL, daily oral consumption of 6 MP along with weekly methotrexate acts as a critical component to cure the disease. For the adequate systemic exposure of 6MP the potential determinants include bioavailability, pharmacogenetics, and adherence to 6-MP[8].

Adherence to 6- MP in patients of ALL, as is the case with other medications which require daily long-term consumption, is complex and requires multidimensional behavior which is based on the child's and parent's understanding and their ability to carry out instructions given by the physicians. Additionally, common instructions of taking 6-MP without food and dairy products and frequent dose adjustments based on the blood counts ,weight/bsa and clinical condition of the child can further complicate the issue of adherence to 6-MP[8].

Adherence to 6-MP has been extensively studied in western countries. In particular, COG studies have elegantly demonstrated increased risk of relapse due to poor adherence and various factors influencing 6-MP adherence[7].

In the study done by Bhatia et al in 2012 ,they found that there was increase in the risk of relapse with decrease in the level of adherence . Further after 4years follow up they even concluded that there was significant increase in the risk of relapse if the adherence rate was <95%. In the patients with <95% adherence rate there was 2.5 fold greater risk of relapse when compared with the patients with >95% adherence and hence they defined patient to be non adherent if the adherence rate <95%. They demonstrated that 44% of the African americans were non adherent to the medication. The incidence of relapse in the study was 17% among the non adherent group and 5%

among the adherent group. In fact they also found that 59% of the patients with relapse were nonadherent[66]. After a follow up of 6.5yrs, <90% was considered the cutoff for adherence, as the risk the relapse was found significant at 90% and the final report of the multivariable regression analysis done in the study showed 3.9 fold increase in the risk of relapse[7].

Further they compared the adherence to 6-mercaptopurine between Hispanic and non- Hispanic white children by using electronic monitoring device (MEMS cap) which records the date and time of each pill box opening and measuring erythrocyte TGN levels in the patients. It was found that the adherence was comparatively low among the Hispanics i.e 88.4%, whereas among the non-Hispanics it was 94.8%, the difference among both the groups was statistically significant. They also assessed the adherence among the patients >12yrs of age, in them Hispanic children (>12yrs) adherence was 85.8% and non-Hispanics (>12yrs) it was 93.1%[66].

In the extended study done by Bhatia et al, it was found that the adherence rate for 6-mercaptopurine among African Americans was 87% and among Asian americans it was 90% which was low when compared with the adherence rate among the non- Hispanics which was 95%[7].

In a study done by Alsous et al, they assessed the adherence of the patients to 6 –mercaptopurine by using a subjective method of using parenteral and children MARS questionnaire and objective method by measuring erythrocyte TGN levels in the patients. They found that by parenteral MARS questionnaire 94.2% were adherent and all the children who answered the questionnaire were adherent (100%). By the objective method 84.6% were adherent. They got an overall adherence rate of 80.8%[10].

In study done by Lennard et al., 1995 about 10% of the patients were nonadherent to 6MP, whereas in some of the studies like de Oliveira et al., 2004; Festa, Tamaroff, Chasalow, & Lanzkowsky, 1992 non adherence was seen in more than 50% of patients[10].

In the other studies the adherence has been monitored by pill counts and self report, which had bias due to patient interference and social desirability respectively. Hence these studies were limited by the poor quality of measures to assess adherence and absence of the clinical basis to define nonaderence.

Adherence to 6MP can be assessed by direct and indirect method. Direct method of adherence is by doing red blood cell assays of 6MP metabolites i.e thioguanine nucleotide, 6-methylthioinosine monophosphate , methylated mercaptopurine, these metabolites will have different concentration patterns in adherent and non adherent patients (Lennard et al., 1995). Cluster analysis of 6-MP metabolites is an established method of assessing adherence objectively. The drawback of objective method is its unavailability and high cost. In contrast, subjective methods are easy to administer and inexpensive. However, they tend to overestimate adherence[8].

Surrogate measures to assess the adherence include neutrophil or total leucocyte count (de Oliveira et al., 2004), and some of the behavioral observations like electronic medication-monitoring devices and pill counts (Lau et al., 1998; Pritchard, Butow, Stevens, & Duley, 2006). Indirect method to assess the adherence consist of patient and/or parent self report, through interviews, questionnaires, and diaries. Both the direct and indirect methods compliment each other in assessing the adherence of the patient to 6MP, so both together will provide as the better adherence rate. As the patient gets only one chance to get cured and prevent the relapse it is very

important to assess the adherence and also explain the patient and the parents about the importance of adherence and it is also important to find ways to improve the adherence[8].

Most of the studies are from western countries, very few studies are from LMIC. In this first Indian study exploring adherence to 6MP in children with ALL, we utilized both subjective and objective methods, as only subjective method of parent or child interview is likely to overestimate adherence (alsous et al)[10]. Subjective assessment of adherence to 6 MP by MMAS on parental interview showed that only 3 (7.5%) had low adherence, 14 (35%) had medium adherence and 23 (57.5%) had high adherence. Children aged more than 10 years were also subjected to adherence test by MMAS.

Objective assessment of baseline adherence by 6TGN and 6MMP levels by cluster analysis, revealed that only 4 (1%) had very low 6TGN & MMP levels . The baseline mean Morisky score was 7.34 ± 0.78 and the baseline median 6 TGN and 6MMP levels were 150 (100,221) and 879 (270,1528) pmol/8×10*8 RBCs, respectively .

On Analysing 3 out of 40(7.5%) children were found to have low adherence (<75%) by MMAS at baseline while RBC metabolites cluster analysis identified one more child (4 out of 40) with poor adherence to 6MP. Our finding of 13 out of 40 children having moderate level of adherence (75% to 90%) is of particular concern. Overall 40% of children were found to have adherence below 90% by MMAS. We could not identify separate RBC metabolite cluster for children with medium adherence measured by MMAS, probably because they were part of large cluster 2 consisting of 30 patients with low 6TGN and 6MMP levels. It is possible that all

those children in cluster 2 were at increased risk of non-adherence as suggested by Bhatia et al[7].

In our study as we used both the objective method (RBC assay) and the subjective method(MMAS) we tried to corelate between both the methods but they were not statistically significant.

In the COG study, difference in the adherence was seen among the ethnic groups, low adherence among the Hispanics was documented when compared with non Hispanic whites. Factors like age of the patient, gender, age of the parents, type of family (nuclear or joint), number of siblings, total number of family members, education and occupation of the parents, distance from the hospital and socioeconomic status were analysed among the groups stratified by the metabolite levels and the MMAS , none of them were statistically significant. This is in contrast with larger COG study which found ethnicity and socioeconomic factors as significantly associated with adherence(Bhatia et al)[7] such as education of the mother, single child household had positive correlation whereas nuclear family house holds, low income households had poor adherence. Our finding of lack of association with these factors could be because of smaller sample size and all our patients were from same ethnic background and low socioeconomic status.

On Further Analysis for the factors in the COG study , the findings suggested that genetic factors also influence relapse in the patients. So low RBC metabolite levels could be explained by ethnicity and pharmacogenomics(Traore et al)[7]. We need larger study to establish RBC metabolite levels and factors responsible for it, during 6MP maintenance therapy in Indian children with ALL.

The metabolism of 6MP intracellularly depends on the activity of TPMT, NUDT 15 and ITPA which can have genetic polymorphism and is correlated to 6TGN

inversely. Among these TPMT is the most widely studied. Among the Caucasian population various alleles of TPMT were seen in 10-15% of them and they required lesser dosing. Whereas among the southeast Asians the prevalence is only 5%. In Indian population the prevalence is <5% [111]. Similarly, in our cohort, we did not find any patient with TPMT polymorphism.

Indian study done by Khera et al in north India revealed 17.5% positive cases of ITPA polymorphism, 9.5% cases were positive for NUDT 15 polymorphism and 3.1% were positive for TPMT polymorphism .These children required lesser cumulative dose, but it was not statistically significant. In our cohort,4 out of 39 patients tested positive for NUDT15*3 polymorphism in heterozygous state. Hence there was higher prevalence of NUDT polymorphisms than TPMT which is in line with other Indian studies[111] . In our study ITPA polymorphism was not done.

Various interventions have been studied to improve adherence to medications which are used chronically with conflicting results[130]. In particular, interventions like mobile text reminders , alarms, parental education have failed to improve adherence in children on 6MP maintenance therapy[130]. However, our simple , affordable, smart pill box with inbuilt alarm significantly improved adherence in our cohort as measured by both methods. 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 a reminder for the patient to take the medication at the scheduled time. The assessment of adherence by MMAS, 6TGN & 6MMP levels after intervention with smart pill box showed statistically significant impact of intervention on improving the adherence. Following intervention, MMAS results illustrated that none had low adherence, 11(27.5%) had medium adherence and 29(72.5%) had high adherence. The mean Morisky score significanty 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). Similarly, on cluster analysis, there was no cluster of patients with very low 6TGN and 6MMP levels. Notably, none of the patient showed poor (<75%) adherence after the intervention. Both the MMAS and median 6TGN 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.

CONCLUSION

In conclusion, non-adherence to 6MP is widely prevalent in Indian children on maintenance treatment for ALL. Simple measures like smart pill box can improve adherence and more such approaches should be studied in LMIC setting.

SUMMARY

- The study was conducted from November 2020 to December 2021 at Paediatric Oncology OPD of a tertiary care hospital
- 40 newly diagnosed cases of ALL between 0 to 18 years of age, who had completed at least one month of maintenance chemotherapy were enrolled in the study.
- Clinical, demographic and laboratory data (CBC, LFT) of recruited children were noted and TPMT and NUDT mutation analysis was done.
- Adherence was assessed first by the subjective method by kannada, marathi, hindi and english translated and validated version of Morisky Medication Adherence Scale (MMAS-8).
- 4ml whole blood was collected from each patient and 6-MP metabolites (6 -TGN and 6-Mmp) in RBCs were measured by a validated method.
- Then Calculating amounts of 6TG and 6MMP in the samples on the basis of comparison of peak intensities with that of the internal standards. Cluster analysis of 6TG and 6MMP levels were used to define whether a patient is adherent or not.
- Parents and older children (>10yrs) were educated and they were provided Istore medicine storage box (smart pill box) with inbuilt alarm.
- After 2 months of intervention, children were assessed again for adherence by above described 2 methods.
- In the study the mean age was 7.39±4.29 and male: female ratio was 1.5:1.
- B ALL was the most common type of ALL(87.50%) and maximum of them belonged to Intermediate risk (77.50%), most of them belonged to M1 cycle in the study

- 5% of the patients were MRD positive.
- All of our patients tested negative for TPMT mutation, 10.26% were positive for NUDT mutation.
- In our study we found that based on the answers given by the parents 50% of the patients had high adherence, 42.5% had medium adherence and 7.5% had low adherence. Based on the answers given by the patients who were >10yrs of age 23.08% of patients had high adherence, whereas 76.2% belonged to medium adherence category.
- Objective method to look for the compliance of the patients to 6-MP was done by measuring the metabolite levels i.e 6 TG levels in the RBC's, it was found that the mean level of 6TG was 215.91±240.20, 75% of the patients were in cluster 2 i.e with low 6 MMP and low 6 TGN.
- Various factors that affects compliance (based on MMAS) were taken into consideration, none of them were found statistically significant.
- After the intervention with the smart pill box and the parent education, there was improvement in the adherence score i.e from 50% to 65% in high adherence group.
- Based on the objective method 92.50% patients were in the low 6MMP and Medium 6TGN suggests that there was improvement in the compliance.
- Baseline median values of 6TG when compared with the follow up values, there was improvement in the levels and it was statistically significant with p value <0.001. There was an increase 6 MMP level between the baseline and follow up it was also statistically significant.

RECOMMENDATIONS

We would like to recommend to do 6 MP metabolite levels for ALL patients in the consolidation phase itself when 6MP is introduced in the treatment as for those who suffer from febrile neutropenia and sepsis as reduction in the 6MP dose according to the metabolite levels can significantly reduce morbidity and mortality. We also recommend to do NUDT mutation, which was seen in 10.26% of our patients, so that we can administer a lower dose to NUDT positive patients and thus prevent complications related to neutropenia due to administration of 6MP.

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LIMITATIONS AND SCOPE OF THE STUDY

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

ANNEXURE I – CONSENT FORM

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
J.N. Medical College, Belagavi
Department of Paediatrics

"Assessment of adherence to 6-mercaptopurine in maintenance phase chemotherapy in children with Acute Lymphoblastic Leukemia- A prospective interventional study"

Principal Investigator: REG NO. BM0120004

Co – investigator (GUIDE): DR _____

Introduction: You are being invited to participate in this study to find out Adherence to 6-mercaptopurine in maintenance phase chemotherapy in children with Acute Lymphoblastic Leukemia. Participation of your child will help us to know the adherence during maintenance phase and factors determining the same. ALL is the commonest malignancy in childhood and 90% of them are long term relapse free survivors. Maintenance phase plays a very important role in the treatment of ALL ,if the patient is not compliant in this phase there are high chances of relapse. The above-mentioned study will therefore help us know the adherence of patient, and will intervene so as to increase compliance and decrease relapse rates. Hence the present study is undertaken. Participation in this study is completely voluntary.

Explanation of procedures: In this study, you will have to answer a few prepared questions regarding your personal experience with your medication(6MP). If you agree to participate, then only questions will be asked to you. At any moment, you can withdraw from the study. Information will be collected using pre-tested-designed questionnaire. The child will be tested for the metabolites of 6MP ie 6TGN levels to look for the compliance once before the start of the study and then they will be educated regarding the importance of the compliance and also will be given pill box ,and they will be monitored every 15 days with

ANC, at the end of 2 months they will be reassessed with questionnaire,6TGN levels.

Possible Benefits: The compliance of the patient will increase and will help to prevent relapse.

Possible Risks: There is no risk involved in this study.

Benefits from the study: We will know the compliance of the patients.

Confidentiality: All the data collected will remain confidential and only aggregated data will be published. Your personal identity will not be revealed.

Withdrawal: Your participation in this study is purely voluntary. You may decide to participate or not. Even though you decide not to participate, you will not be deprived of the benefits of this study.

Costs of Participation: The cost of the study will be borne by the subjects if they can afford. If not, it will be borne by the researcher. It involves the cost of 6TGN levels and the pill box. There will be no additional cost to you for participating in this study.

Payment of Participation: There will be no incentives to you for participating in this study.

Questions: If you have any questions regarding the study, you should contact Principal Investigator **REG NO. BM0120004 admission batch,** Department of Paediatrics. J. N. Medical College, Belagavi, 590010, Ph. No- _____

Guide: _____, Hematooncologist, Associate Professor, Department of Paediatrics, J. N. Medical College, Belagavi, 590010.

If you have any questions about your rights as a study participant, you may contact **DR HARSHA HEGDE,** Chairperson, JNMC, IEC & Scientist D, ICMR, National Institute of Traditional Medicine Belgaum- 9480422500

Legal Rights: By signing this consent form; you are not waiving any of your Legal rights.

Consent statement:

"I volunteer and consent to participate in the study. I have read (or it has been read to me in the language known to me) the information sheet thoroughly. Full opportunity was given to me to ask questions. I am fully satisfied with the answers to the questions I wanted to ask. I hereby voluntarily agree to participate in this research project".

Name of the Participant	Signature of the participant or Left-Hand Thumb impression
Name of Investigator	Signature of investigator
Name of Witness	Signature of Witness
Date:	Place:

Assent (<18 years)

I have read the information in this form. After understanding all details about the study, I agree to give assent to be included as a volunteer in the study titled "**Assessment of adherence to 6-mercaptopurine in maintenance phase chemotherapy in children with Acute Lymphoblastic Leukemia- A prospective interventional study"**

Name of the Participant	Signature of the participant or Left-Hand Thumb impression
Name of the Parent	Signature of the parent
Name of Investigator	Signature of investigator
Name of Witness	Signature of Witness

Date: _____ Place: _____

ANNEXURE II – PROFORMA

Assessment of adherence to 6-mercaptopurine in maintenance phase chemotherapy in children with Acute Lymphoblastic Leukemia- A prospective interventional study"

Principal Investigator: REG NO. BM0120004

Co – investigator (GUIDE) : DR _____

Name of the patient:

Age: Gender:

Patient hospital no:

Address:

Distance from kle hospital:

Phone number:

Anthropometry

Weight : Height: BMI(for children>5yrs): BSA:

Diagnosis: B-ALL: T-ALL:

Date of diagnosis:

Risk stratification :

As per NCI: Treatment risk stratification:

Post induction MRD status:

Date of initiation of Maintainence chemotherapy:

Current number of Maintainence cycle:

Dose of 6mp as per BSA: Total dose:

Dose of methotrexate as per BSA: Total dose:

TPMT mutation status: Positive: negative:

Date of collection of first sample/ date of enrollment in the study:

Proposed date of collection of second sample:

Baseline morisky score : Parent: Patient(if age >10 yrs):

Morisky score on follow up(after 2 months): Parent:

patient (if age >10 yrs):

Baseline levels: 6TGN: 6MMP:

Follow up levels: 6TGN: 6MMP:

Baseline CBC at the time of collection of 1st sample: Hb: TLC: ANC: Platelet count:

CBC at the time of collection of 2nd sample: Hb: TLC: ANC: Platelet count:

Mean ANC over 2 months:

Baseline & follow up LFT:

Any interruption in maintainence chemotherapy: Yes: no:

If yes then duration: Cause:

Any features of drug toxicity:

Satisfactory usage of smart pill box: yes: no:

Demographic details of patient and family:

Ethnicity:

H/o consanguinity: yes: no:

Family history of cancer: yes: no:

No of siblings:

Socio economic status as per modified bg prasad:

Parent's details

Mother	father
Name:	name:
Age :	age:
Education:	education:

Type of family:

Total number of family members:

Morisky Medication Adherence Scale (MMAS)

For caregiver

1. Do you sometimes forget to give medications?	YES	NO
2. People sometimes miss giving medications for reasons other than forgetting. Thinking over the past two weeks , were there any days when you did not give the medications?	YES	NO
3. Have you ever cut back or stopped giving medications without telling your doctor , because the child felt worse when he/she took it?	YES	NO
4. When you travel or leave home with the child ,do you sometimes forget to bring along child's medications?	YES	NO
5. Did you give the medications yesterday?	YES	NO
6. When you feel like the child's health condition is under control , do you sometimes stop giving the medications to the child?	YES	NO
7. Giving medications everyday Is a real inconvenience for some people . Do you ever feel hassled about sticking to the child's treatment plan?	YES	NO
8. How often do you have difficulty remembering to give the medications?	Never/Rarely	4
	Once in a while	3
	Sometimes	2
	Usually	1
	All the time	0

Morisky Medication Adherence Scale (MMAS)

For Patient

1. Do you sometimes forget to take medications?	YES	NO
2. People sometimes miss taking medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take the medications?	YES	NO
3. Have you ever cut back or stopped taking medications without telling your doctor, because you felt worse when you took it?	YES	NO
4. When you travel or leave home, do you sometimes forget to bring along the medications?	YES	NO
5. Did you take the medications yesterday?	YES	NO
6. When you feel like your health condition is under control , do you sometimes stop taking the medications ?	YES	NO
7. Taking medications everyday Is a real inconvenience for some people. Do you ever feel hassled about sticking to the treatment plan?	YES	NO
8. How often do you have difficulty remembering to take the medications?	Never/Rarely	4
	Once in a while	3
	Sometimes	2
	Usually	1
	All the time	0

SLNO	NAME OF F	AGE	GENDER	PATIENT H(	ADDRESS	DISTANCE F	PH NUMBER	WEIGHT
1	Sangamesh	6	Male	5509737	Madarkhar	170km	9901375457	19kg
2	Shrusti	11	Female	5325514	Bagalkot	200km	9535045691	45kg
3	Bhagyashre	11	Female	5000865	Tarihal,bel	15km	9880648009	21kg
4	Praneet	4	Male	5661020	Bellavadi	70km	9632035200	14kg
5	Aaradhya V	6.5	Female	5337171	Belagavi	40km	9448420415	16.5kg
6	Pritam Bira	5	Male	5498020	Harugeri,R	100km	9591851895	14.7kg
7	Mohamma	15	Male	5168138	Ujwal naga	4km	7411772221	46.5kg
8	Swati N Mu	7	Female	5705174	Bharat galli,Belagavi		8197559018	18.5kg
9	Tejashwini	13	Female	5444482	Mattikoppa	30km	9900432174	37.7kg
10	Sampatha I	7	Male	5104637	Babaleshw	200km	9901896749	16.9kg
11	Deepa Mar	11	Female	5198569	A/P Lakhan	100km	9980160282	16kg
12	Prajwal K P	7	Male	5112270	A/P Hiremu	110km	7353341170	18.3kg
13	Sandeep Sa	14	Male	4826054	Athani talu	110km	9036194844	31kg
14	Pallavi Y Hc	15	Female	5446944	yaragatti,b	120km	8660400220	44kg
15	Suraj R Pati	9	Male	5090615	Gallagali	160km	9980482950	
16	Pranay	6	Male	4833714	Sankeshwa	100km	8277110606	16kg
17	Kaveri rudr	9	Female	4983871	Dastikoppa	60km	9743110801	21.7kg
18	Ahmed Raz	3.9	Male	5153148	Belagavi	3km	7760461986	15kg
19	Anand Mah	3	Male	5677259	Mudhol,Be	150km	7483583329	10kg
20	Aliza tanve	4	Female	5352793	Belagavi	10km	9743687453	11.9kg
21	Akshata	5	Female	5126838	kittur		9740083579	13kg
22	Pranav V A	5	Male	5302307	Jamkhandi	120km	7829539278	19.5kg
23	Atharv Vitt	11	Male	5538086	Kallehol,Be	10km	9538008010	22.4kg
24	Vedant Pra	7	Male	5679954	14,SBI colo	9km	8762813005	18.2kg
25	Prapti Para	2	Female	5223231	Vantamuri	10km	9483460973	12kg
26	Sanjay	6	Male	5679991	Ilkal	220km	9482084569	20kg
27	Saad	3	Male	943060	gokak	65km	9060512744	12.5kg
28	Pratistha B	5	Female	5688130	Sutatti,Raibag taluk,be		9739056377	15kg
29	Ashwini	7	Female	5668478	Bagalkot	100km	9986832914	17kg
30	Shourya	4 1/2	Male	5730882	Jamkhandi	146km	9482374173	13kg
31	Sanvi M	4	Female	5725067	navalgund	150km	9682569935	14kg
32	Dnyaneshw	9	Male	5678548	Sangankeri	70km	9886716462	18.2kg
33	Laxmi	15	Female	5758689	Kittur	50km	9972215268	63.3kg
34	Sanvi sindh	3	Female	5428876	Sindhur tot	140km	7676748510	12kg
35	Bhirappa	11	Male	5725964	Athani talu	180km	9686737575	27kg
36	Ramu	12	Male	5817534	gokak	100km	9632357423	32kg
37	Saba	14	Female	5762974	Jamkhandi	160km	9741418947	36kg
38	Darshan	17	Male	5780195	Akkatangih	40km	9591659990	45kg
39	Advik	3	Male	5847221	Kougalgi	70km	9740473380	13kg
40	Rajveer	1.5	Male	5865913	Nippani	75km	9611490143	8.3kg
41	Anvit	2	Male	5899590	Haveri	200km	9620325466	9kg
42	Mohamma	5	Male	5929502	A/P Boragc	200km	7022521910	13.8kg
43	Haider ali	3	male	5927512	Vijayapur	200km	7996178389	11.8kg
	Dnyaneshwar							
	Aaradhya k							

Ahmed

HEIGHT	BMI	BSA	DIAGNOSIS	DATE OF DIA	RISK STRAT	POST INDU	DATE OF INI	CURRENT M
106cm	16.9	0.74	B-ALL	30-11-2019	Intermedia	Negative	15-06-2020	M2
140cm	22.9	1.3	B-ALL	12-07-2019	Intermedia	Negative	03-02-2020	M4
118cm	15	0.8	B-ALL	22-10-2018	Intermedia	Negative	16-05-2019	M7
88cm	18	0.58	B-ALL	16-03-2020	Intermedia	Negative	06-10-2020	M1
109cm	13.8	0.7	B-ALL	22-07-2019	Intermedia	Negative	05-02-2020	M4
98cm	15.3	0.63	B-ALL	21-11-2019	Intermedia	Negative	18-06-2020	M2
157cm	18.8	1.4	B-ALL	14-03-2019	Intermedia	Negative	26-10-2019	M5
113cm	14.4	0.75	B-ALL	05-04-2018	Intermedia	Negative	19-11-2018	M8
148cm	17.2	1.24	B-ALL	09-10-2019	Intermedia	Negative	17-04-2020	M3
107cm	14.7	0.7	B-ALL		High	Positive	24-08-2019	M6
122cm	10.7	0.73	T-ALL	17-03-2019	High	Positive	10-10-2019	M5
114cm	14	0.75	B-ALL	31-01-2019	Intermedia	Negative	12-10-2019	M5
147cm	14.3	1.12	B-ALL	15-02-2019	Intermedia	Negative	19-09-2019	M6
144cm	21.2	1.32	B-ALL	11-10-2019	Intermedia	Negative	18-05-2020	M3
			B-ALL	09-01-2019	Intermedia	Negative		
104cm	14.7	0.67	B-ALL	07-06-2018	Intermedia	Negative	23-01-2019	M7
120cm	15	0.84	B-ALL	11-10-2018	Intermedia	Negative	21-05-2019	M7
93cm	17.3	0.62	B-ALL	21-03-2019	Intermedia	Negative	30-08-2019	M6
86cm		0.47	B-ALL	23-03-2020	Intermedia	Negative	16-09-2020	M1
86cm		0.52	B-ALL	01-08-2019	Intermedia	Negative		M5
97cm		0.6	B-ALL		Intermedia	Negative		M5
110cm		0.77	B-ALL	24-06-2019	Intermedia	Negative	13-01-2020	M4
118cm	16.08	0.85	B-ALL	18-12-2019	High	Negative	05-10-2020	M2
107cm	15.3	0.73	B-ALL	17-04-2020	Intermedia	Negative	09-11-2020	M1
85cm		0.53	B-ALL	19-04-2019	Intermedia	Negative	05-12-2019	M5
106cm	17.7	0.76	T-ALL	14-04-2020	High	Negative	20-11-2020	M1
94cm		0.56	B-ALL		Intermedia	Negative		
99cm		0.64	B-ALL	06-05-2020	Intermedia	Negative	07-12-2020	M1
100cm	17	0.68	B-ALL	18-03-2020	Intermedia	Negative	27-11-2020	M1
97cm		0.56	B-ALL	29-06-2021	Intermedia	Negative	22-01-2021	M1
98cm		0.61	T-ALL	11-06-2020	High	Negative	11-02-2021	M2
112cm	14.5	0.75	B-ALL	22-06-2020	High		21-01-2021	M2
148cm	28.8	1.6	T-ALL	28-05-2020	High	Negative	21-01-2021	M1
89cm		0.53	B-ALL	23-09-2019	Intermedia	Negative	15-04-2020	M4
135cm	14.8	1	B-ALL		High	Negative	17-02-2021	M2
132cm	18.3	1.1	B-ALL	01-09-2020	Intermedia	Negative	21-04-2021	M2
151cm	15.7	1.2	B-ALL	25-05-2020	High	Negative	12-02-2021	M2
175cm	14.6	1.47	T-ALL	23-07-2020	High	Negative	19-05-2021	M1
44cm		0.58	B-ALL	30-09-2020	Intermedia	Negative	03-05-2021	M1
77cm		0.42	B-ALL	20-10-2020	Intermedia	Negative	13-05-2021	M1
79cm		0.44	B-ALL	21-11-2020	Intermedia	Negative	08-06-2021	M1
100cm		0.61	B-ALL	22-12-2021	Intermedia	Negative	26-06-2021	M1
88cm		0.53	B-ALL	18-12-2020	Intermedia	Negative	14-06-2021	M1

DOSE OF 6MP		DOSE OF METHOTREX/		TPMT MUT	NUDT Muta	DATE OF COI	PROPOSED D	MORISKY S
BSA	TOTAL	BSA	TOTAL					BASELINE
44.4		14.6		Negative	positive	03-11-2020	04-01-2021	8
78	68	26		Negative	positive	04-11-2020	04-01-2021	8
48	50	16		Negative	Negative	05-11-2020	05-01-2021	6.75
34.8	42	11.6		Negative	Negative	06-11-2020	06-01-2021	6.25
42	32	14		Negative	Negative	07-11-2020	07-01-2021	8
37.8	32	12.6		Negative	Negative	09-11-2020	09-01-2021	5.5
84	78	28		Negative	negative	10-11-2020	10-01-2021	8
45	42	15		Negative	positive	10-11-2020	10-01-2021	7
74.4	70	24.8		Negative	Negative	13-11-2020	13-01-2021	6.25
42	38	14		Negative	Negative	17-11-2020	18-01-2021	7
43.8	40	14.6		Negative	Negative	17-11-2020	18-01-2021	8
45	40	15		Negative	Negative	17-11-2020	18-01-2021	5.75
67.2	60	22.4		Negative	Negative	17-11-2020	18-01-2021	8
79.2	70	26.4		Negative	Negative	18-11-2020	18-01-2021	8
				Negative	Negative	18-11-2020	18-01-2021	6.5
40.2	42	13.4		Negative	Negative	19-11-2020	19-01-2021	5.5
50.4	48	16.8		Negative	Negative	25-11-2020	25-01-2021	5.75
37.2	32	12.4		Negative	Negative	27-11-2020	27-01-2021	7.25
28.2	42.3	9.4		Negative	Negative	30-11-2020	30-01-2021	5.75
31.2	32	10.4		Negative	Negative	30-11-2020	30-01-2021	8
36	35.5	12		Negative	Negative	30-11-2020	30-01-2021	6.5
46.2	43.5	15.4		Negative	Negative	04-01-2021	04-03-2021	8
51	50.2	17		Negative	Negative	05-01-2021	05-03-2021	8
43.8	42.2	14.6		Negative	Negative	08-01-2021	08-03-2021	8
31.8	30	10.6		Negative	positive	08-01-2021	08-03-2021	8
45.6	40	15.2		Negative	Negative	20-01-2021	20-03-2021	8
33.6	35.5	11.2		Negative	Negative	09-02-2021	09-04-2021	7.75
38.4	36	12.8		Negative	Negative	10-02-2021	10-04-2021	7
40.8	38	13.6		Negative	Negative	12-02-2021	12-04-2021	8
33.6	32	11.2		Negative	Negative	19-02-2021	19-04-2021	6.5
36.6	35	12.2		Negative	Negative	12-05-2021	12-07-2021	8
45	35	15		Negative	Negative	09-03-2021	09-05-2021	8
96	36	32		Negative	Negative	25-03-2021	25-05-2021	8
31.8	30	10.6		Negative	Negative	21-04-2021	21-06-2021	7
60	42	20		Negative	Negative	18-05-2021	18-07-2021	6.75
66	35	22		Negative	Negative	21-05-2021	21-07-2021	8
72	42	24		Negative	negative	15-06-2021	15-08-2021	8
88.2	54	29.4		Negative	Negative	18-06-2021	18-08-2021	7
34.6	32	11.6		Negative	Negative	30-06-2021	30-08-2021	8
25.2	32	8.4		Negative	Negative	21-06-2021	21-08-2021	8
26.4	34	8.8		Negative	Negative	08-07-2021	08-09-2021	7
36.6	35	12.2		Negative		02-09-2021	02-11-2021	6.75
31.8	35.8	10.6		Negative		08-07-2021	08-09-2021	6.5
	34			Negative	Negative			
				Negative	Negative			

CALE(PAREI	MORISKY SCORE OF PA		6TGN LEVELS		6MMP LEVELS		BASELINE CBC	
FOLLOW U	BASELINE	FOLLOW U	BASELINE	FOLLOW U	BASELINE	FOLLOW U	HB	TLC
8							12.2	2500
7.75	8	8					11.7	4100
6	7.75	8					12	2100
8							11.8	2800
8							13.9	3000
7							12.2	3400
7	8	7					12.7	2200
8							10.2	2200
6.25	6.25	6.25					12.3	2800
7							11.9	3900
8	7.75	8					10.8	3300
8							10.1	2200
8	7	8					12	3100
8	6.75	8					13.2	2600
8							13.3	4500
7.75							11.9	3400
7.75							9.9	2800
8							10.9	4700
8							12.1	1900
8							12.4	4100
7.5							11.3	6000
8							12.8	5800
7.75	7.75	7.75					10.5	4100
8							12.3	2200
8							8.6	3100
8							10.6	1300
8							12.9	4400
8							13	4400
8							11.1	4100
8							10.6	3900
8							10.7	4200
8							9.4	1900
8	7	8					10.6	3000
7							8.3	1600
8	6.75	8					9.1	2800
8	8	8					10.8	4800
8	8	8					12.1	3500
8	7.75	8					7.2	4500
7							10	3300
7							11	6300
8							11.1	3600
8							10.7	1700
7							9.9	7000

			FOLLOW UP CBC			MEAN ANC	BASELINE LFT	
ANC	PLATLET CC	HB	TLC	ANC	PLATLET COUNT	SGOT	SGPT	
1500	228	11.4	1800	900	317	1010	90	114
2400	193	11.7	3200	1800	281	1975	25	44
1500	205	10.5	3600	2600	196	1370	40	84
2016	243	11.9	3500	2100	287	2250	38	66
1200	361	11.4	2200	1000	341	1125	29	35
1500	366	11.4	3200	1800	351	1746	42	40
1300	267	9.3	500	100	139	1042	62	108
1200	222	8	900	500	357	1210	24	39
1700	239	11.3	500	100	153	1616	117	300
2400	264	7.2	1500	400	143	1857	302	303
1300	265	10.3	3300	1800	378	2100	84	151
1700	209	8.1	2900	900	362	1190	220	258
1800	267	11.7	1100	500	287	1700	44	80
1900	222	10.5	1200	700	195	1390	66	96
2800	215	13	2400	1200	280	1710	44	85
1400	310	10.4	2400	1500	379	1180	27	43
1500	165	11.5	2800	1300	240	1800	165	318
2600	388	10	3300	1700	281	1692	31	33
600	508	11.9	2400	1000	580	1660	28	24
2500	339	10.6	2700	300	220	2166	122	223
4700	193	10.9	3400	1800	221	1607	178	401
4100	371	11	2600	1200	351	1822	81	188
3000	380	10.7	1400	800	193	1342	62	52
1200	257	11.4	2100	1000	273	1255	50	88
1300	248						15	7
700	201	10.3	1200	600	278	1700	48	92
2200	470	11.1	700	300	106	1630	37	48
323	180						29	33
1800	271	11.5	7600	4300	312	1970	37	36
1900	259	10.7	2300	700	46	29	36	30
2900	449	11.5	1500	400	350	1060	16	20
800	281	9.6	1500	400	270	1450	23	28
2100	293	9.9	1400	700	239	1450	27	17
900	200	8.3	1300	800	205	1775	49	76
1200	201	10.2	8700	6800	223	3016	32	24
2200	392	12	4200	1500	402	2650	31	17
2000	338	11.4	5400	4400	262	2828	166	192
3800	368	8.5	4000	2900	411	2085	18	15
2100	221	9.4	2300	1400	179	1640	142	328
4600	396	11.4	4500	2400	229	1766	39	33
1300	211	10.7	2600	900	165	1300	39	46
321	900	10.8	2800	1600	347	1060	27	44
5200	320	8.7	1600	700	474		43	29

FOLLOWUP LFT		ANY INTERI	DURATION	CAUSE OF I	ANY FEATU	SATISFACT(	ETHINICITY	H/O CONSA
SGOT	SGPT							
43	121	NO			nil	yes	Indian	No
36	33	YES	17DAYS	low count	nil	yes	Indian	No
32	27			forgetfulness		yes	Indian	No
44	81	NO		forgetfulness		yes	Indian,linga	No
25	26	NO				yes	Indian,hind	No
55	48			forgetfulness		yes	Indian,hind	No
27	92						Indian,mus	No
17	11						Indian,mar	No
86	212						Indian,hind	No
192	265						Indian,2A	No
149	271						Indian,2A	yes
34	30			forgetfulness			Indian,hind	No
22	89	no		travel	nil	yes	Indian,sc	No
44	67			forgetfulness		no	Indian,hind	yes
58	85			forgetfulness			Indian	No
21	43			forgetfulness			Indian,hind	yes
30	26	no		forgetfulne	nil	yes	Indian,hind	No
37	23					yes	Indian,mus	No
38	51			forgetfulness			Indian.cat 1	No
30	34					yes	Indian,mus	No
64	43	NO		forgetfulness		NO	Indian	no
258	515						Indian,jain	yes
54	162					yes	Indian,mar	No
65	120	no			nil	yes	indian,hind	no
							Indian,hind	No
197	98	no			nil	yes	Indian,hind	yes
126	223	no		forgetfulness		yes	Indian,mus	no
							Indian,jain	no
23	8	no				yes	Indian	yes
62	927	no		travel		yes	Indian,hind	no
33	98	no				yes	Indian	no
33	58					yes	hindu	no
45	27	yes		forgetfulne	nil	no	Hindu	no
38	37			forgetfulness		yes	Hindu linga	yes
30	77	yes		forgetfulne	nil	yes	Hindu	no
22	32	no			nil	yes	Hindu	no
		no			nil	yes	Muslim	yes
19	10	yes	2 days	side effects		yes	Hindu	no
249	628				nil	yes	Hindu linga	no
41	32	yes	7days		nil	no	Maratha	no
32	18			side effects		no	Hindu	no
42	104			travel		no	Muslim	no
6	11					no	Hindu	yes

FAMILY H/(	NUMBER O	SOCIOECOI	TYPE OF FA	TOTAL NUI	MOTHER'S DETAILS			FAT
					NAME	AGE	EDUCATIOI	NAME
Yes	2	III	Joint	12	Madhuri	32yrs	12 std	Basavaraj
No	2	IV	Nuclear	5	Sapna	35rs	10std	Gurunath
Yes	2	IV	Nuclear	5	Mahadevi	45yrs	5std	Siddhayya
Yes	0	V	Joint	5	Kamakshi	22yrs	BA	Basavanay
No	1	I	Nuclear	5	Snehalata	37yrs	12std	Vijaykumar
No	2	IV	Joint	6	Nimbavva	28yrs	5std	Shivanand
No	3	V	Nuclear	5	Nazneem	42yrs	10std	Mallikjan
No	2	II	Joint	7	Jayashree	29yrs	12std	Nagendra
No	3	II	Nuclear	6	Shivaleela	35yrs	10std	Basavaraj
No	1	III	Joint	8	Rukmini	23yrs	10th std	Basavant
No	1	IV	Joint	6	Manju	35yrs	Illiterate	Manjunath
No	2	IV	Nuclear	5	Lakshmi	32yrs	1std	Kashinath
No	1	III	Nuclear	4	Lakshmi	36yrs	12thstd	Sanjay
No	3	V	Nuclear	8	Parvati	35yrs	Illiterate	Yamanappa
No	2	IV	Nuclear	5	Savita	35yrs	10thstd	Ramesh
Yes	1	III	Nuclear	4	Pooja	32yrs	10thstd	Sunil
Yes	1	IV	Nuclear	5	Geeta	32yrs	3thstd	Rudrappa
No	1	III	Nuclear	4	Asiya	35yrs	12thstd	Yusuf
No	2	III	Joint	11	Geeta	24yrs	10thstd	Mahadev
No	1	III	Nuclear	4	Fareen	28yrs	10thstd	Tanveer
no	1	IV	Nuclear	4	Hema	28yrs	7th std	Ramesh
No	1	V	Joint	13	Praneeta	27yrs	10thstd	Vrushab
No	1	III	Joint	5	Ranjana	30yrs	8thstd	Parasuram
no	1	II	Joint	6	Shraddha	33yrs	BE	Praveen
No	1	II	Nuclear	5	Priyanka	25yrs	9thstd	Parashuran
No	2	I	Nuclear	5	Shanta	28yrs	12thstd	Basavaraj
no	1	II	Nuclear	4	Sania	28yrs	8th std	Mohamme
no	1	IV	Joint	8	Rani	32yrs	BA	Pramod
no	2	V	Joint	11	Renuka	30yrs	10th std	Govind
no	0	III	Nuclear	3	Madhu	26yrs	10th std	Ramesh
no	1	I	Nuclear	4	Manjula	30yrs	Bed	Shivayoggi
no	3	V	Nuclear	6	Mayavva	35yrs	Illiterate	Anand
yes	2	V	Nuclear	6	Drakshini	37yrs	10th std	Manjunath
no	2	V	Nuclear	4	Prema	23yrs	8thstd	Shridhar
no	1	IV	Joint	13	Savitri	30yrs	5thstd	Appasaab
no	2	V	Joint	25	Sangeeta	26yrs	5thstd	Suresh
no	3	IV	Nuclear	6	Raziya	32yrs	7thstd	Malik
no	1	V	Nuclear	4	Jayashree	35yrs	SSLC	Ningappa
no	1	V	Joint	9	Sahana	29yrs	BA	Mahantesh
no	1	V	Joint	9	Pooja	27yrs	B pharma	Sandeep
no	0	III	Joint	5	Bhavya	23yrs	PUC	Elokoti
no	1	V	Nuclear	4	Masabi	30yrs	8thstd	Faruq
no	2	IV	Nuclear	5	Dilshad	29yrs	10th std	Mehaboob

THER'S DETAILS

AGE	EDUCATION
41yrs	BA
42yrs	Illiterate
48yrs	10std
36yrs	12std
38ys	BA
35yrs	10std
50yrs	12std
39yrs	10std
52yrs	BA
30yrs	12thstd
36yrs	BA
40yrs	5th std
40yrs	5thstd
40yrs	Illiterate
42yrs	12thstd
34yrs	12thstd
45yrs	7thstd
42yrs	12thstd
32yrs	B.com
40yrs	10thstd
35yrs	12th std
33yrs	BA
32yrs	7thstd
41yrs	BE
35yrs	10thstd
40yrs	B.ph
30yrs	8th std
35yrs	M.com
33yrs	Illiterate
30yrs	12th std
35yrs	12th std
35yrs	7thstd
41yrs	10th std
died	
38yrs	7th std
28yrs	10th std
38yrs	4th std
50yrs	12th std
33yrs	BAMS
32yrs	12th std
32yrs	BA
31yrs	8thstd
34yrs	Illiterate

SLNO	AGE	GENDER	PATIENT HOSPITAL NUMBER	ADDRESS	DISTANCE FROM KLE HOSPITAL	PH NUMBER	WEIGHT	HEIGHT	BMI	BSA	DIAGNOSIS	DATE OF DIAGNOSIS	RISK STRATIFICATION	POST INDUCTION MRD STATUS	DATE OF INITIATION OF MAINTENANCE	CURRENT NUMBER OF MAINTENANCE CYCLE	DOSE OF 6MP		DOSE OF METHOTREXATE	
																	BSA	TOTAL	BSA	TOTAL
1	6	Male	5509737	Madarkhandi,Jamkhandi	170km	9901375457	19kg	106cm	16.9	0.74	B-ALL	30-11-2019	Intermediate	Negative	15-06-2020	M2	44.4	21.6	14.6	20
2	11	Female	5325514	Bagalkot	200km	9535045691	45kg	140cm	22.9	1.3	B-ALL	12-07-2019	Intermediate	Negative	03-02-2020	M4	78	50.2	26	30
3	4	Male	5661020	Bellavadi	70km	9632035200	14kg	88cm	18	0.58	B-ALL	16-03-2020	Intermediate	Negative	06-10-2020	M1	34.8	36	11.6	20
4	6.5	Female	5337171	Belagavi	40km	9448420415	16.5kg	109cm	13.8	0.7	B-ALL	22-07-2019	Intermediate	Negative	05-02-2020	M4	42	31.5	14	25
5	5	Male	5498020	Harugeri,Raibag,Belagavi	100km	9591851895	14.7kg	98cm	15.3	0.63	B-ALL	21-11-2019	Intermediate	Negative	18-06-2020	M2	37.8	36	12.6	20
6	13	Female	5444482	Mattikoppa,Bailhongal,Belagavi	30km	9900432174	37.7kg	148cm	17.2	1.24	B-ALL	09-10-2019	Intermediate	Negative	17-04-2020	M3	74.4	78.2	24.8	30
7	7	Male	5112270	A/P Hiremulangi post Idgal,Ramdurg	110km	7353341170	18.3kg	114cm	14	0.75	B-ALL	31-01-2019	Intermediate	Negative	12-10-2019	M5	45	46	15	20
8	3	Male	5677259	Mudhol,Belagavi	150km	7483583329	10kg	86cm		0.47	B-ALL	23-03-2020	Intermediate	Negative	16-09-2020	M1	28.2	43.8	9.4	25
9	5	Female	5126838	kittur	50km	9740083579	13kg	97cm		0.6	B-ALL	15-04-2019	Intermediate	Negative	28-11-2019	M5	36	32	12	20
10	5	Male	5302307	Jamkhandi	120km	7829539278	19.5kg	110cm		0.77	B-ALL	24-06-2019	Intermediate	Negative	13-01-2020	M4	46.2	37.3	15.4	30
11	11	Male	5538086	Kallehol,Belagavi	10km	9538008010	22.4kg	118cm	16.08	0.85	B-ALL	18-12-2019	High	Negative	05-10-2020	M2	51	54	17	25
12	7	Male	5679954	14,SBI colony,RC nagar,1st stage,belagavi	9km	8762813005	18.2kg	107cm	15.3	0.73	B-ALL	17-04-2020	Intermediate	Negative	09-11-2020	M1	43.8	41.12	14.6	25
13	2	Female	5223231	Vantamuri colony,belagavi	10km	9483460973	12kg	85cm		0.53	B-ALL	19-04-2019	Intermediate	Negative	05-12-2019	M5	31.8	38	10.6	20
14	6	Male	5679991	Ilkal	220km	9482084569	20kg	106cm	17.7	0.76	T-ALL	14-04-2020	High	Negative	20-11-2020	M1	45.6	48	15.2	20
15	3	Male	943060	gokak	65km	9060512744	12.5kg	94cm		0.56	B-ALL	20-10-2018	Intermediate	Negative	21-08-2019	M7	33.6	35	11.2	15
16	5	Female	5688130	Sutatti,Raibag taluk,belagavi		9739056377	15kg	99cm		0.64	B-ALL	06-05-2020	Intermediate	Negative	07-12-2020	M1	38.4	30.08	12.8	25
17	7	Female	5668478	Bagalkot	100km	9986832914	17kg	100cm	17	0.68	B-ALL	18-03-2020	Intermediate	Negative	27-11-2020	M1	40.8	42	13.6	20
18	4 1/2	Male	5730882	Jamkhandi	146km	9482374173	13kg	97cm		0.56	B-ALL	29-06-2021	Intermediate	Negative	22-01-2021	M1	33.6	38	11.2	15
19	4	Female	5725067	navalgund	150km	9682569935	14kg	98cm		0.61	T-ALL	11-06-2020	High	Negative	11-02-2021	M2	36.6	45.2	12.2	20
20	9	Male	5678548	Sangankeri	70km	9886716462	18.2kg	112cm	14.5	0.75	B-ALL	22-06-2020	High	Negative	21-01-2021	M2	45	50.2	15	20
21	15	Female	5758689	Kittur	50km	9972215268	63.3kg	148cm	28.8	1.6	T-ALL	28-05-2020	High	Negative	21-01-2021	M1	96	73.8	32	45
22	11	Male	5725964	Athani taluk	180km	9686737575	27kg	138cm	14.8	1	B-ALL	16-08-2020	High	Negative	17-02-2021	M2	60	68.8	20	35
23	3	Male	5847221	Kougalgi	70km	9740473380	13kg	44cm		0.58	B-ALL	30-09-2020	Intermediate	Negative	03-05-2021	M1	34.6	46	11.6	20
24	1.5	Male	5865913	Nippani	75km	9611490143	8.3kg	77cm		0.42	B-ALL	20-10-2020	Intermediate	Negative	13-05-2021	M1	25.2	28.8	8.4	15
25	3	male	5927512	Vijayapur	200km	7996178389	11.8kg	88cm		0.53	B-ALL	18-12-2020	Intermediate	Negative	14-06-2021	M1	31.8	30.2	10.6	15
26	11	male	6049883	Kolapur	100km		32kg	132cm	18.3	1.08	B-ALL	07-04-2021	Intermediate	Negative	25-10-2021	M2	64.8	54.4	21.6	30
27	4	female	6119697	Dharwad	100km		13kg	100cm		0.6	B-ALL	19-06-2021	Intermediate	Negative	08-01-2022	M1	36	42.5	12	20
28	3	Male	5678548	Belagavi	50km	8095494786	11kg	87cm		0.5	B-ALL	27-08-2020	Intermediate	Negative	20-03-2021	M7	30	34.54	10	20
29	15	Male	5168138	Ujwal nagar,Belagavi	4km	7411772221	46.5kg	157cm	18.8	1.4	B-ALL	14-03-2019	Intermediate	Negative	26-10-2019	M5	84	78	28	35
30	11	Female	5000865	Tarihal,belagavi taluk	15km	9880648009	21kg	118cm	15	0.8	B-ALL	22-10-2018	Intermediate	Negative	16-05-2019	M7	48	50	16	20
31	7	Female	5705174	Bharat galli,Belagavi		8197559018	18.5kg	113cm	14.4	0.75	B-ALL	05-04-2018	Intermediate	Negative	19-11-2018	M8	45	42	15	20
32	7	Male	5104637	Babaleshwar, Vijayapur	200km	9901896749	16.9kg	107cm	14.7	0.7	B-ALL	20-10-2018	High	Positive	24-08-2019	M6	42	38	14	20
33	11	Female	5198569	A/P Lakhanayakanakoppa,Ramdurg taluk	100km	9980160282	16kg	122cm	10.7	0.73	T-ALL	17-03-2019	High	Positive	10-10-2019	M5	43.8	40	14.6	20
34	14	Male	4826054	Athani taluk,Hugarpur	110km	9036194844	31kg	147cm	14.3	1.12	B-ALL	15-02-2019	Intermediate	Negative	19-09-2019	M6	67.2	60	22.4	25
35	15	Female	5446944	yaragatti,banatti,bagalkot	120km	8660400220	44kg	144cm	21.2	1.32	B-ALL	11-10-2019	Intermediate	Negative	18-05-2020	M3	79.2	70	26.4	35
38	17	Male	5780195	Akkatangihal	40km	9591659990	45kg	175cm	14.6	1.47	T-ALL	23-07-2020	High	Negative	19-05-2021	M1	88.2	54	29.4	35
37	3.9	Male	5153148	Belagavi	3km	7760461986	15kg	93cm	17.3	0.62	B-ALL	21-03-2019	Intermediate	Negative	30-08-2019	M6	37.2	32	12.4	20
38	4	Female	5352793	Belagavi	10km	9743687453	11.9kg	86cm		0.52	B-ALL	01-08-2019	Intermediate	Negative	02-02-2020	M5	31.2	32	10.4	15
39	3	Female	5428876	Sindhur tota,tungal taluk, jamakhandi	140km	7676748510	12kg	89cm		0.53	B-ALL	23-09-2019	Intermediate	Negative	15-04-2020	M4	31.8	30	10.6	20
40	12	Male	5817534	gokak	100km	9632357423	32kg	132cm	18.3	1.1	B-ALL	01-09-2020	Intermediate	Negative	21-04-2021	M2	66	35	22	35

TPMT MUTATION STATUS	NUDT Mutation	DATE OF COLLECTION OF FIRST SAMPLE	PROPOSED DATE OF COLLECTION OF SECOND SAMPLE	MORISKY SCALE(PARENT)		MORISKY SCORE OF PATIENT (>10YRS)		BASELINE CBC						FOLLOW UP CBC						MEAN ANC OVER 2 MONTHS	BASELINE LFT		FOLLOWUP LFT		ANY INTERRUPTION IN MAINTENANCE PHASE
				BASELINE	FOLLOW UP	BASELINE	FOLLOW UP	HB	TLC	ANC	RBC count	PCV	PLATLET COUNT	HB	TLC	ANC	RBC count	PCV	PLATLET COUNT		SGOT	SGPT	SGOT	SGPT	
Negative	positive	03-11-2020	04-01-2021	8	8			9.7	2200	1300	3.9	29.1	243	11.9	1500	800	4.34	35.7	230	1200	38	60	22	182	NO
Negative	positive	04-11-2020	04-01-2021	8	7.8	8	8	8.3	3000	1800	2.6	24.9	191	10.5	3800	2200	3.47	31.5	312	2300	31	57	30	32	YES
Negative	Negative	06-11-2020	06-01-2021	6.25	8			11	6100	5400	3.7	33	254	11.2	4200	3200	3.68	33.6	173	3525	69	181	68	160	NO
Negative	Negative	07-11-2020	07-01-2021	8	8			13	2400	1400	4.3	39	277	10.8	2000	800	3.8	32.4	380	914	79	93	21	11	NO
Negative	Negative	09-11-2020	09-01-2021	5.5	7			10	4300	2500	4	30	708	11.6	5000	3800	3.92	34.8	495	3166	25	12	97	42	
Negative	Negative	13-11-2020	13-01-2021	6.25	6.3	6.25	6.25	11	1300	800	3.7	33	170	11.6	1500	1000	3.89	34.8	250	1683	12	7	20	17	
Negative	Negative	17-11-2020	18-01-2021	5.75	8			10	1200	800	4.7	30	207	10.9	3300	1800	4.69	32.7	237	1600	36	33	30	32	
Negative	Negative	30-11-2020	30-01-2021	5.75	8			8.7	2600	1700	3.1	26.1	174	8.1	1200	700	2.77	24.3	214	2125	28	16	31	29	
Negative	Negative	30-11-2020	30-01-2021	6.5	7.5			11	2400	900	3.6	33	141	10.2	2700	1300	3.13	30.6	310	1600	53	107	50	52	NO
Negative	Negative	04-01-2021	04-03-2021	8	8			11	4100	2500	3.9	33	267	11.4	2800	1500	4.16	34.2	292	1666	100	82	189	270	
Negative	Negative	05-01-2021	05-03-2021	8	7.8	7.75	7.75	11	2000	1000	3.4	33	245	7.1	1200	400	2.1	21.3	296	2655	201	302	16	10	
Negative	Negative	08-01-2021	08-03-2021	8	8			12	2300	1300	4	36	234	11	1400	600	3.86	33	245	1533	46	75	30	56	no
Negative	positive	08-01-2021	08-03-2021	8	8			9.3	6300	2000	3.3	27.9	319	11.3	14400	12700	4.18	33.9	310	4200	18	14	20	22	
Negative	Negative	20-01-2021	20-03-2021	8	8			11	2600	1900	3.5	33	182	9.3	3100	2200	2.86	27.9	178	1620	155	315	24	33	no
Negative	Negative	09-02-2021	09-04-2021	7.75	8			12	4000	2000	3.9	36	530	12	3100	1500	3.94	36	296	1900	28	30	30	32	no
Negative	Negative	10-02-2021	10-04-2021	7	8			11	2900	1100	4	33	243	12.3	2700	1400	3.98	36.9	218	1640	125	274	120	280	
Negative	Negative	12-02-2021	12-04-2021	8	8			8.3	4900	1800	2.7	24.9	226	10.3	4200	2000	3.26	51.5	191	2640	23	8	146	100	no
Negative	Negative	19-02-2021	19-04-2021	6.5	8			10	2700	1100	4.1	30	260	7.5	2300	800	3.07	22.5	321	1550	153	226	19	11	no
Negative	Negative	12-05-2021	12-07-2021	8	8			10	3000	1900	3.4	30	351	11.2	2700	1500	3.41	33.6	229	1150	20	12	134	57	no
Negative	Negative	09-03-2021	09-05-2021	8	8			9.5	2500	1700	2.7	28.5	249	3.1	1600	800	0.35	9.3	149	1660	25	26	29	23	
Negative	Negative	25-03-2021	25-05-2021	8	8	7	8	10	4200	2800	3.5	30	270	10.2	2800	1700	3.5	30.6	295	2450	27	13	20	10	yes
Negative	Negative	18-05-2021	18-07-2021	6.75	8	6.75	8	8.6	4600	2900	4.4	25.8	211	9.4	6000	1900	4.5	28.2	240	1866	21	38	40	32	yes
Negative	Negative	30-06-2021	30-08-2021	8	7			9.3	3300	2100	4.8	27.9	290	8	1600	800	3.81	24	288	2050	108	166	25	33	
Negative	Negative	21-06-2021	21-08-2021	8	7			11	5300	3300	4	33	471	11	3000	1500	3.93	33	449	1328	33	17	31	32	yes
Negative		08-07-2021	08-09-2021	6.5	7			9.9	3000	1800	3.4	29.7	357	8.4	1900	1000	2.85	25.2	63	2166	11	6	38	23	
Negative	Negative	16-03-2022	21-05-2022	7	7	7.5	8	12	2300	1300	4.5	36	345	12.3	2400	1600	4.54	36..9	253	1400	60	107	50	52	
Negative	Negative	17-03-2022	19-05-2022	7.5	8			13	2400	1400	3.8	39	277	10.8	2000	800	3.71	32.4	380	985	60	107	50	52	
Negative	Negative	16-03-2022	16-05-2022	6.5	7			11	3100	1400	3.4	33	333	10.4	1500	1000	3.94	31.2	169	2028	45	32	54	53	
Negative	negative	10-11-2020	10-01-2021	8	7	8	7	13	2200	1300	3.5	39	267	9.3	500	100	3.1	27.9	139	1042	62	108	27	92	
Negative	Negative	05-11-2020	05-01-2021	6.75	6	7.75	8	12	2100	1500	4	36	205	10.5	3600	2600	3.5	31.5	196	1370	40	84	32	27	
Negative	positive	10-11-2020	10-01-2021	7	8			10	2200	1200	3.2	30	222	8	900	500	3	24	357	1210	24	39	17	11	
Negative	Negative	17-11-2020	18-01-2021	7	7			12	3900	2400	3.5	36	264	7.2	1500	400	2.8	21.6	143	1857	302	303	192	265	
Negative	Negative	17-11-2020	18-01-2021	8	8	7.75	8	11	3300	1300	3.5	33	265	10.3	3300	1800	3.3	30.9	378	2100	84	151	149	271	
Negative	Negative	17-11-2020	18-01-2021	8	8	7	8	12	3100	1800	4.2	36	267	11.7	1100	500	3.4	35.1	287	1700	44	80	22	89	no
Negative	Negative	18-11-2020	18-01-2021	8	8	6.75	8	13	2600	1900	3.6	39	222	10.5	1200	700	4.1	31.5	195	1390	66	96	44	67	
Negative	Negative	18-06-2021	18-08-2021	7	8	7.75	8	7.2	4500	3800	3.1	21.6	368	8.5	4000	2900	3.2	25.5	411	2085	18	15	19	10	yes
Negative	Negative	27-11-2020	27-01-2021	7.25	8			11	4700	2600	4.2	33	388	10	3300	1700	3.6	30	281	1692	31	33	37	23	
Negative	Negative	30-11-2020	30-01-2021	8	8			12	4100	2500	4.5	36	339	10.6	2700	300	3.6	31.8	220	2166	122	223	30	34	
Negative	Negative	21-04-2021	21-06-2021	7	7			8.3	1600	900	3.2	24.9	200	8.3	1300	800	3.2	24.9	205	1775	49	76	38	37	
Negative	Negative	21-05-2021	21-07-2021	8	8	8	8	11	4800	2200	3.5	33	392	12	4200	1500	4.4	36	402	2650	31	17	22	32	no
				7.34	7.7	7.4	7.7692																		

DURATION OF INTERRUPTION	CAUSE OF INTERRUPTION	ANY FEATURES OF DRUG TOXICITY	SATISFACTORY USAGE OF SMART PILL BOX	ETHINICITY	H/O CONSANGUINITY	FAMILY H/O CANCER	NUMBER OF SIBLINGS	SOCIOECONOMIC STATUS	TYPE OF FAMILY	TOTAL NUMBER OF FAMILY MEMBERS	MOTHER'S DETAILS			FATHER'S DETAILS			Baseline	FU	Baseline	FU
											NAME	AGE	EDUCATION	NAME	AGE	EDUCATION	6 TG in pmol/8×10*8		6 MMP	
		nil	yes	Indian	No	Yes	2	III	Joint	12	Madhuri	32yrs	12 std	Basavaraj	41yrs	BA	160	232	817	697
17DAYS	low count	nil	yes	Indian	No	No	2	IV	Nuclear	5	Sapna	35rs	10std	Gurunath	42yrs	Illiterate	166	220	253	1615
	forgetfulness		yes	Indian,lingayat	No	Yes	0	V	Joint	5	Kamakshi	22yrs	BA	Basavanayya	36yrs	12std	81.4	231	1528	486
			yes	Indian,hindu panchal	No	No	1	I	Nuclear	5	Snehalata	37yrs	12std	Vijaykumar	38ys	BA	283	253	1070	1176
	forgetfulness		yes	Indian,hindu kurubara	No	No	2	IV	Joint	6	Nimbavva	28yrs	5std	Shivanand	35yrs	10std	1152	272	299	217
				Indian,hindu lingayat	No	No	3	II	Nuclear	6	Shivaleela	35yrs	10std	Basavaraj	52yrs	BA	244	329	88	760
	forgetfulness			Indian,hindu kshtriya	No	No	2	IV	Nuclear	5	Lakshmi	32yrs	1std	Kashinath	40yrs	5th std	113	178	2045	3626
	forgetfulness			Indian.cat 1	No	No	2	III	Joint	11	Geeta	24yrs	10thstd	Mahadev	32yrs	B.com	175	219	1006	1183
	forgetfulness		NO	Indian	no	no	1	IV	Nuclear	4	Hema	28yrs	7th std	Ramesh	35yrs	12th std	163	509	1215	2020
				Indian,jain	yes	No	1	V	Joint	13	Praneeta	27yrs	10thstd	Vrushab	33yrs	BA	221	455	672	667
			yes	Indian,maratha	No	No	1	III	Joint	5	Ranjana	30yrs	8thstd	Parasuram	32yrs	7thstd	82	182	1657	3576
		nil	yes	indian,hindu	no	no	1	II	Joint	6	Shraddha	33yrs	BE	Praveen	41yrs	BE	117	280	893	3473
				Indian,hindu	No	No	1	II	Nuclear	5	Priyanka	25yrs	9thstd	Parashuram	35yrs	10thstd	143	267	319	1678
		nil	yes	Indian,hindu lingayat	yes	No	2	I	Nuclear	5	Shanta	28yrs	12thstd	Basavaraj	40yrs	B.ph	245	314	1437	1944
	forgetfulness		yes	Indian,muslim	no	no	1	II	Nuclear	4	Sania	28yrs	8th std	Mohammed	30yrs	8th std	121	318	2188	2660
				Indian,jain	no	no	1	IV	Joint	8	Rani	32yrs	BA	Pramod	35yrs	M.com	207	201	2619	3200
			yes	Indian	yes	no	2	V	Joint	11	Renuka	30yrs	10th std	Govind	33yrs	Illiterate	157	377	1441	2037
	travel		yes	Indian,hindu	no	no	0	III	Nuclear	3	Madhu	26yrs	10th std	Ramesh	30yrs	12th std	123	185	3521	3543
			yes	Indian	no	no	1	I	Nuclear	4	Manjula	30yrs	Bed	Shivayoggi	35yrs	12th std	235	271	3307	4075
			yes	hindu	no	no	3	V	Nuclear	6	Mayavva	35yrs	Illiterate	Anand	35yrs	7thstd	105	546	1470	28738
	forgetfulness	nil	no	Hindu	no	yes	2	V	Nuclear	6	Drakshini	37yrs	10th std	Manjunath	41yrs	10th std	163	251	471	5366
	forgetfulness	nil	yes	Hindu	no	no	1	IV	Joint	13	Savitri	30yrs	5thstd	Appasaab	38yrs	7th std	100	193	867	528
		nil	yes	Hindu lingayat	no	no	1	V	Joint	9	Sahana	29yrs	BA	Mahantesh	33yrs	BAMS	101	147	270	918
7days		nil	no	Maratha	no	no	1	V	Joint	9	Pooja	27yrs	B pharma	Sandeep	32yrs	12th std	85	304	3691	3541
			no	Hindu	yes	no	2	IV	Nuclear	5	Dilshad	29yrs	10th std	Mehaboob	34yrs	Illiterate	99	221	6757	2033
				Hindu	No	no	1	IV	Nuclear	3	Renuka	28yrs	10th std	ramesh	34yrs	10thsd	1284	215	7474	3493
				Hindu	no	no	1	I	Nuclear	3	hema	28yrs	12th std	sunil	30yrs	b com	204	212	3931	3950
				Muslim	no	no	2	IV	Joint	6	hamida	29yrs	5thstd	mohammed	32yrs	5th std	147	190	879	2064
				Indian,muslim	No	No	3	V	Nuclear	5	Nazneem	42yrs	10std	Mallikjan	50yrs	12std	160	200	252	820
	forgetfulness		yes	Indian	No	Yes	2	IV	Nuclear	5	Mahadevi	45yrs	5std	Siddhayya	48yrs	10std	100	150	225	320
				Indian,maratha	No	No	2	II	Joint	7	Jayashree	29yrs	12std	Nagendra	39yrs	10std	240	310	610	850
				Indian,2A	No	No	1	III	Joint	8	Rukmini	23yrs	10th std	Basavant	30yrs	12thstd	142	264	310	1500
				Indian,2A	yes	No	1	IV	Joint	6	Manju	35yrs	Illiterate	Manjunath	36yrs	BA	220	315	470	920
	travel	nil	yes	Indian,sc	No	No	1	III	Nuclear	4	Lakshmi	36yrs	12thstd	Sanjay	40yrs	5thstd	242	310	1102	1200
	forgetfulness		no	Indian,hindu sampagar	yes	No	3	V	Nuclear	8	Parvati	35yrs	Illiterate	Yamanappa	40yrs	Illiterate	98	150	3201	4020
2 days	side effects		yes	Hindu	no	no	1	V	Nuclear	4	Jayashree	35yrs	SSLC	Ningappa	50yrs	12th std	250	245	320	1502
			yes	Indian,muslim	No	No	1	III	Nuclear	4	Asiya	35yrs	12thstd	Yusuf	42yrs	12thstd	235	270	1440	2030
			yes	Indian,muslim	No	No	1	III	Nuclear	4	Fareen	28yrs	10thstd	Tanveer	40yrs	10thstd	102	150	255	620
	forgetfulness		yes	Hindu lingayat	yes	no	2	V	Nuclear	4	Prema	23yrs	8thstd	Shridhar	died		150	352	1322	1560
		nil	yes	Hindu	no	no	2	V	Joint	25	Sangeeta	26yrs	5thstd	Suresh	28yrs	10th std	221	316	450	900