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ORIGINAL ARTICLE

Evaluation of FTO polymorphism in 6-mercaptopurine related intolerance in children with acute lymphoblastic leukemia

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Abstract

Purpose Thiopurine drugs like 6-Mercaptopurine (6MP) are the cornerstone of maintenance therapy in acute lymphoblastic leukemia (ALL). A recently described variant in alpha-ketoglutarate dependent dioxygenase (*FTO*) gene has been reported to play an important role in thiopurine induced myelosuppression.

Methods In this study, we genotyped a coding variant (p.Ala134Thr, rs79206939) and an intronic variant (rs16952570) of *FTO* in 174 Indian children (age ≤ 12 years) with ALL on maintenance phase of chemotherapy and examined correlation with the risk of thiopurine induced myelosuppression and hepatic toxicity.

Results The prevalence of *FTO*-rs16952570 polymorphism was 18.4% (32/174) with 142 (82%) cases having TT genotype, 26 (15%) cases with TC genotype and 6 (3.4%) cases having CC genotype. *FTO*-rs79206939 was absent and non-polymorphic in our study group. The mean dose of 6-MP during 36 weeks of maintenance of TT, TC and CC carriers of *FTO*-rs16952570 was 53.7, 53.6 and 54.1 mg/m^2/day. Number of patients tolerating starting dose of 60 mg/m^2/day was significantly higher in CC (50%) than TT/TC (14%) genotype carrying cases ($p = 0.014$). However, no statistical significance was observed for total leukocyte count (TLC), absolute neutrophil count (ANC) as well as for platelets counts in patients harboring *FTO*-rs16952570 TT/TC/CC genotype at 4, 8, 12, 24 and 36 weeks after start of thiopurine therapy. Further, no significant correlation was noted between number of weeks of chemotherapy interruptions or episodes of febrile neutropenia and no evidence of hepatotoxicity was found with the genotype studied.

Conclusion Polymorphism in *FTO*-rs16952570 did not show any correlation with thiopurine related toxicity in ALL patients.

Keywords ALL · Thiopurine · Maintenance phase · Chemotherapy · IBD

Introduction

Acute lymphoblastic leukemia is the most common childhood cancer, accounting for 25% of all malignancies in childhood, with peak incidence between two and five years of age [1]. The survival rates of childhood ALL have approached around 90% in recent studies due to better risk stratification involving genetic characteristics of leukemic cells, modification of therapy based on patient pharmacogenomics, and improved supportive care of patients [2].

The maintenance phase of treatment of ALL is the longest with oral thiopurines given for a period of 2–2.5 years. Thiopurines are metabolized through a series of reactions involving enzymes of the purine salvage pathway [3]. The thiopurine metabolism enzymes are known to harbor genetic variations that have long been implicated in the toxicity of thiopurines, the most significant being the single nucleotide polymorphism (SNP) involving the enzyme *TPMT* [4]. SNPs in *TPMT* are more prevalent in the Caucasian population and dose reductions based on *TPMT* levels have been incorporated in many leukemia protocols [5]. The other enzyme implicated in increasing the risk of thiopurine toxicity especially in Asian and Hispanic ancestry is *NUDT15* [6–8]. *NUDT15* polymorphism is observed in 12% in our population [9–11]. Around 30% of our ALL cohort has been

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observed to suffer from thiopurine toxicity. Therefore, there is a need of further studies and identification of other variants which may be responsible for thiopurine toxicity.

To identify novel genetic variants associated with toxicity to thiopurines, recent genome wide association studies have shown that a coding and an intronic variant in fat mass and obesity-associated (*FTO*) gene is significantly associated with the risk of thiopurine induced leukopenia in patients with inflammatory bowel disease (IBD) [12]. Another study has demonstrated a protective effect of the presence of intronic variant of *FTO* against thiopurine induced leukopenia in IBD [13]. Considering the controversial reports regarding this gene, we examined the frequency of *FTO* gene mutation in our cohort to evaluate its role in thiopurine toxicity. To our knowledge, this is the first study reporting the correlation between thiopurine induced toxicity in ALL patients with *FTO* gene variants.

Methods

Patients and treatment

Pediatric ALL patients (age ≤ 12 years) undergoing maintenance therapy were enrolled prospectively in the study. The patients were risk stratified and treated as per Indian Childhood Collaborative Leukemia Group 2015-ICICLE protocol (Clinical Trials Registry-India (CTRI) CTRI/2015/12/006434) [14]. Informed consent was obtained from the patients or their guardians. The study was approved by the hospital ethics committee.

The maintenance phase includes daily 6-mercaptopurine (6MP), weekly oral methotrexate (MTX) along with an intrathecal MTX at 3-monthly intervals as per the ICICLE protocol. 6MP and MTX was started at the recommended starting doses being 60 mg/m^2/day and 20 mg/m^2/, respectively. Blood sample for genotyping was drawn prior to starting maintenance therapy. The enrolled patients were followed with a complete blood count done every 2 weeks and liver function tests done 3 monthly. Side effect profile included; (1) myelosuppression (absolute neutrophil count-ANC < 750/mm^3, and/or thrombocytopenia-platelets count < 75,000/mm^3), (2) occurrence of febrile neutropenia (temperature higher than 38 °C with ANC < 500/mm^3 or ANC showing a falling trend to reach < 500/mm^3), (3) hepatotoxicity {an increase of the liver enzyme alanine transferase (ALT) to at least 5 times(> 44 U/L) and /or rise of serum bilirubin beyond 3 times the upper limit of normal} and (4) duration of treatment interruptions; were recorded for 36 weeks. Dose adjustment, if any, was done as per routine in the pediatric oncology clinic to maintain an ANC between 750 and 1500/mm^3.

Genotyping

Approximately 2 ml of peripheral blood was collected from enrolled patients in sodium EDTA tubes. DNA was extracted using the QIAmp DNA blood kit (Qiagen Inc.) as per the manufacturer's instructions. *FTO* (rs79206939& rs16952570) genotyping was performed by Real-Time PCR based on competitive allele-specific PCR. The SNP positive cases and randomly selected negative cases were further confirmed by Sanger sequencing using ABI 3500 genetic analyzer (Applied Biosystems).

Statistical analysis

Statistical analysis was performed using IBM SPSS software version 22.0. Allelic and genotypic frequencies were noted. Baseline characteristics, 6MP related toxicities and genotypes were compared using Student *t* test and two-sided Fisher's exact test or Chi- Square test for continuous and categorical data respectively. The association of the different genotypes with 6MP related febrile neutropenia and hepatotoxicity was evaluated using the Mann Whitney *U* test. *P* value < 0.05 was considered as statistically significant.

Results

Patient demographics and clinical characteristics

A total of 200 children (age ≤ 12 years) undergoing maintenance phase chemotherapy according to ICICLE 2015 protocol in the study period between January 2016 and August 2021 were randomly enrolled in the study. Twenty six cases were excluded from the analysis due to insufficient DNA or loss of follow up. One hundred and seventy four patients underwent genotyping and were monitored for 6MP related toxicity profile for 36 weeks. The median follow up of the cohort was 29 months following start of maintenance therapy. The demographics and clinical characteristics of patients ($n = 174$) are listed in Table 1. The cohort comprised of patients with a mean age of 5 years (SD ± 3 years) with a male to female ratio of 2.4:1. One hundred and fifty cases were B-cell ALL (86%) and 24 were T-cell ALL (14%). According to ICICLE risk stratification 65 (37.3%) cases were standard risk, 32 (18.4%) were intermediate and 78 (44.2%) were high risk cases.

6MP dose and toxicity profile

The mean dose of 6MP in the studied cohort was 53.7 mg/m^2/day (SD ± 6) and cumulative mean dose over 36 weeks

Table 1 Baseline clinical characteristics of the cohort ($N=174$)

Clinical parameters	Cohort ($n=174$)	Neutropenia ($n=58$)	No Neutropenia ($n=116$)	p value
Age (in years) at start of therapy, median (range 1–12 years)	5	4	5	0.22
Gender, *n* (%)				
Male	123 (71%)	43 (74%)	80 (69%)	0.14
Female	51 (29%)	15 (26%)	36 (31%)	
ALL diagnosis, *n* (%)				
B-cell ALL	150 (86%)	50 (86%)	100 (86%)	–
T-cell ALL	24 (14%)	8 (14%)	16 (14%)	
ICICLE risk group, *n* (%)				
Standard risk	65 (37.4%)	24 (41%)	41 (35%)	0.34
Intermediate risk	32 (18.4%)	8 (14%)	24 (21%)	
High risk	77 (44.3%)	26 (45%)	51 (44%)	
6-MP dose in mg/m^2/day, mean (SD)	53.7 (±6.62)	52.9 (±8.0)	54.1 (±5.7)	**0.039**
6-MP cumulative dose (mg/m^2), mean (36 weeks); (SD)	12,382 (±1831)	11,470 (±2015)	12,836 (±1550)	**0.031**
Weeks off-therapy, (SD)	3 (±2.6)	5 (±2.6)	2 (±1.9)	**0.02**
Baseline TLC in /mm^3, mean (SD)	4413 (±2325)	4386 (±2246)	4425 (±2371)	0.7
Baseline ANC in /mm^3, mean (SD)	1618(±1015)	1544 (±1074)	1653 (±989)	0.8
Baseline platelets in $\times 10^3$/mm^3, mean (SD)	296 (±136)	306 (±153)	291 (±127)	0.07

Results with significant values are highlighted in bold

ALL acute lymphoblastic leukemia, *ICICLE* Indian Childhood Collaborative Leukemia group, *6MP* 6-mercaptopurine, *SD* standard deviation, *TLC* total leukocyte count, *ANC* absolute neutrophil count

was 12382 mg/m^2. Sixty percent of cases tolerated more than 80% ($n=105$) of planned dose of 6MP while only 2% ($n=3$) of cases tolerated less than 50% of planned dose and the remaining 38% ($n=66$) cases tolerated doses between 50 and 80% of planned dose. Fifty-eight out of 174 (33.3%) patients developed at least one neutropenic episode. The average daily dose of cases having at least one episode of neutropenia was 52.9 mg/m^2/day compared to 54.1 mg/m^2/day for cases having no neutropenia ($p=0.039$). The mean weeks of off therapy in the cohort was noted to be 5 weeks for cases developing neutropenia compared to 2 weeks of off therapy for patients having no neutropenia ($p=0.02$). The hepatotoxicity profile was monitored for 36 weeks. Though transaminases were mildly raised in 18 patients and serum bilirubin was abnormal in 3 cases, no patient required cessation of therapy owing to hepatotoxicity.

Genotype

Observed frequencies of the *FTO* variants are shown in Table 2. The coding variant p.Ala134Thr of *FTO* (rs79206939) was absent and non-polymorphic in our study cohort. The prevalence of *FTO* intronic variant (rs16952570) was 18.4% ($n=32$) with 82% ($n=142$) TT (wild type)

Table 2 *FTO* rs16952570 genotype association with 6MP related toxicity in pediatric ALL ($N=174$)

Parameters	Genotype frequency ($N=174$)			p value
	TT $N=142$ (82%)	TC $N=26$ (15%)	CC $N=6$(3%)	
6MP dose in mg/m^2/day, mean (SD)	53.7 (±6.6)	53.6 (±5.78)	54.1 (±9.3)	0.98
6MP cumulative dose (mg/m^2), mean (36 weeks) (SD)	12,366 (±1872)	12,516 (±1909)	12,126 (±1073)	0.87
Patients tolerating 6MP dose of ≥60 mg/m^2/day (*N*)	20	3	3	0.04
	23		3	0.014
Febrile neutropenia episodes, mean weeks (SD)	0.55 (±1)	0.38 (±0.5)	0.1 (±1)	0.37
Weeks off-therapy, mean (SD)	3.12 (±2.6)	2.62(±1.9)	4 (±3.2)	0.44
Baseline TLC in /mm^3, mean (SD)	4471 (±2387)	4181 (±1909)	3916 (±1750)	0.75
Baseline ANC in /mm^3, mean (SD)	1663 (±1043)	1513 (±502)	954 (±487)	0.216
Baseline platelets in $\times 10^3$/mm^3, mean (SD)	293 (±143)	320 (±76)	265 (±96)	0.597

6MP 6-mercaptopurine, *SD* standard deviation, *TLC* total leukocyte count, *ANC* absolute neutrophil count

carriers 82%, 15% ($n=26$) TC carriers and CC carriers were 3% ($n=6$) noted. The minor allele frequency (C) was 0.11.

Effect of *FTO* variant rs16952570 on 6MP related toxicity

The mean dose of 6MP over 36 weeks of maintenance phase for *FTO* rs16952570 TT carriers was 53.7 mg/m^2/day, for CC carriers was 54.1 mg/m^2/day for TC carriers was 53.6 mg/m^2/day (Table 2). Number of patients tolerating starting dose of 60 mg/m^2/day was significantly higher in CC (50%) than TT/TC (14%) genotype carrying cases ($p=0.014$). The total leukocyte count (TLC), absolute neutrophil count (ANC) and platelets count observed during 4, 8, 12, 24 and 36 weeks of follow up after start of thiopurine therapy in patients harboring *FTO* rs16952570 TT, TC and CC genotypes is shown in Fig. 1. However, no statistical difference could be sought. Further, a trend of lower platelets counts in CC patients, similar to that of TLC and ANC levels (Fig. 1) was also noted at different time points. No significant correlation was observed with hepatotoxicity among the 3 genotypes for a follow up of 36 weeks.

Discussion

Maintenance phase of chemotherapy seems to be one of the most important and most challenging phases of chemotherapy in ALL [15], with strict monitoring of counts being vital toward reducing the risk of relapse [16, 17]. It is also one of the most difficult phases of chemotherapy because of the wide variability in dosing in different protocols and inter-individual variations in 6MP/MTX bioavailability and pharmacokinetics [18]. All these factors in combination cause patients receiving identical doses per body surface area to experience very different systemic and intracellular drug exposures [19]. An estimated 20–25% of children being treated for ALL experience severe drug related toxicities [15]. Identification of the high risk children prone to severe adverse drug effects and tailoring therapy accordingly helps in reducing the therapy interruptions in the children and ensures good compliance ultimately resulting in the reduced rates of relapse [2, 15].

One of the most common reasons for interpatient variability in drug response is gene polymorphisms in thiopurine metabolism pathway. SNPs in the *FTO* gene have been recently implicated in thiopurine induced myelosuppression [12, 20]. An intronic variant (rs16952570) and a coding variant (rs79206939, p.A134T) have been found to be significantly associated with the risk of thiopurine induced myelosuppression [12, 13]. In the present study we evaluated the association of the presence of these variants and the risk of thiopurine toxicity in children with ALL undergoing maintenance phase of therapy. We found that coding variant (rs79206939, p.A134T) was non-polymorphic in our cohort. Similar report was provided by Chen S et al. in their study showing that this variant is not present in the Indian sub-population [13]. It has been reported that the *FTO* rs79206939 is absent in several 1000 Genome Project populations, namely European-Caucasians, Africans, and South Asians and low in East Asians (2.2%) [12]. This would explain the absence of this variant in our study population as it was an ethnically homogenous population comprising of only Indians. Thus, considering the low frequency of (rs79206939, p.A134T) across different ethnicity, its potential to be considered as biomarker for thiopurine generated leukopenia is very low, despite its association with myelosupression as reported previously [10].

The prevalence of non-coding variant of *FTO* rs16952570 in our study cohort was 18%. Similar frequency was reported by Chen et al. [13]. We further examined the association of *FTO* rs16952570 with thiopurine induced toxicity. We did not find any statistically significant difference in the dose of 6MP, febrile neutropenia episodes and weeks off therapy among the genotypes. In the study by Chen et al. the protective nature of *FTO* rs16952570 variant was suggested in their cohort of IBD patients [13]. Though we did note slightly higher mean dose of 6MP during 36 weeks of maintenance in CC carriers (54.1 mg/m^2/day) and the number of patients tolerating starting dose (60 mg/m^2/day or higher) higher in CC (50%) than TT/TC (14%) genotype carrying

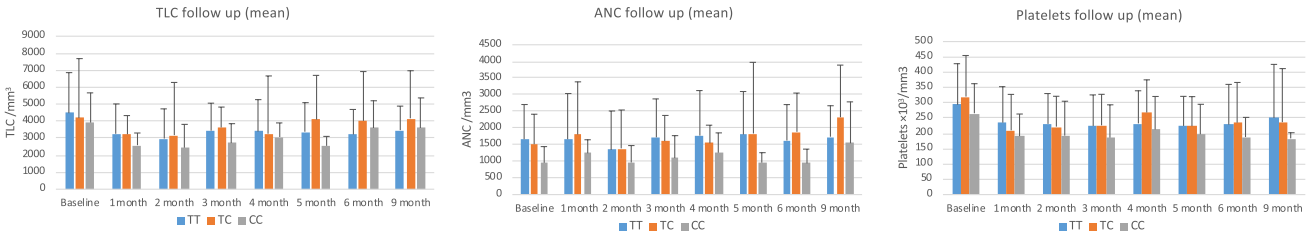

Fig. 1 TLC, ANC and platelets counts at baseline and after 1, 2, 3, 4, 5, 6 and 9 months of thiopurine therapy in *FTO* rs16952570 genotype carriers. *TLC* total leukocyte count, *ANC* absolute neutrophil count

cases ($p = 0.014$), no further parameters was suggestive of the protective profile of this polymorphism in relation to myelosupression or hepatotoxicity in ALL patients.

We further looked at the TLC, ANC and platelets counts before and after 4, 8, 12, 24 and 36 weeks of start of maintenance therapy. We noted that the TT and TC alleles carrying patients had higher TLC, ANC and platelets counts compared to CC genotype throughout the period of follow up of 9 months (Fig. 1a, b, c). Peculiarly, patients with the CC genotype had lower ANC/TLC/platelets at baseline or starting of maintenance therapy. This is indicative of the fact that these patients may have lower threshold to chemotherapeutics agents that remains consistent though out the therapy and also contributes toward masking the 6-MP related myelosuppression. This data could be correlated to study by Kim et al. where they have shown that *FTO* rs16952570 is strongly linked to rs79206939, p.A134T and there is a strong association with thiopurine induced leukopenia [12]. Further, our data are contrary to the previous report by Chen et al. where they noted that CC carrying patients have significantly higher TLC, ANC and platelets counts than TT and TC variant carrying IBD patients before and after 4, 8, 12 weeks of thiopurine therapy [13]. There could be a number of reasons for the difference noted in the thiopurine related toxicity in genotypes of FTO between the two reports. One reason could the ethnicity of the two population, where this particular variant may be forming a haplotype with other SNPs resulting in different outcomes. Further, due to different protocols of treatment being followed, patients of these two cohorts may show different drug response and treatment related toxicity, as the combination of drugs and duration given to patient may vary.

Recently, *FTO* gene has been identified as RNA modifier and have been shown to govern normal haematopoiesis and leukemogenesis [21]. *FTO* has been reported to be upregulated in many tumors and its high expression represents an independent risk factor of shorter overall survival in multiple types of cancer patients [22–25]. The consistent lower TLC, ANC and platelets in CC carrying is suggestive of involvement of *FTO* rs16952570 in regulation of *FTO* protein expression in cells which may further result in alteration in haematopoiesis and possibly leukemogenesis. The role of *FTO* in the thiopurine metabolic pathway remains undefined and warrants further investigation considering its functional role as demethylase that may serve to regulate the nucleotide pools for DNA and RNA synthesis as well.

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Data availability Data will be made available on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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