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Original Article

Safety and efficacy of azathioprine in immune thrombocytopenia

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Abstract: Background: Immune thrombocytopenia (ITP) is a benign hematological disorder characterized by low platelet counts in peripheral blood and spectrum of various bleeding manifestations. Azathioprine is one of the effective, readily available, and affordable immunosupressants available for ITP management in developing countries. We aimed to study the efficacy and long-term safety profile of our patients with ITP who were treated with azathioprine. Method: This was a retrospective, single-center study conducted at a tertiary care hospital in Northern India. The patients who had received at least one line of therapy before receiving azathioprine were included in this study. All patients received oral azathioprine at a dose of 1 mg/kg/day (50 mg or 100 mg tablet formulations were used), which was increased up to 2 mg/kg/day depending upon the response and adverse effects. Result: Sixty-three patients were analyzed. Their median age was 28 years (range 15-68); 29/63 patients (46.03%) were females. The median duration from diagnosis to azathioprine initiation was 539 days (323 days-980.5 days). The patients included in the study had received a median of 3 (range 1-6) prior lines of therapies; 38/63 patients (60.32%) had received ≥3 prior therapies. Six patients (9.5%) had relapsed after splenectomy, and 16 patients (25.4%) had relapsed after receiving rituximab. The mean baseline platelet count was 10000/μL. The median time to response was 95 days (90 days-not reached) and the cumulative overall response rate (complete and partial response) at day 90 was 38.1%. Only one patient achieved complete response with azathioprine in our study. The cumulative rate of relapse at five years was 21.2%. Twenty-six patients stopped azathioprine after achieving some response (CR/PR) with Azathioprine for a median duration of 1067.5 days (range: 236 days-2465 days). They were followed up for a median of 870 days (range: 392 days-1928 days), and twelve of them relapsed. Twenty-six patients (26/63, 41.27%) reported one or more adverse events while on azathioprine. Leucopenia was the most frequent adverse event, followed by anemia and hepatobiliary laboratory abnormalities. Serious adverse events (grade ≥3 CTCAEv4) were noted in three patients (4.7%). One patient succumbed to severe sepsis multiorgan dysfunction while being on treatment. Conclusion: We conclude that azathioprine has a good response rate in chronic ITP patients. It is well-tolerated with minimal and manageable side effects.

Keywords: Azathioprine, thrombocytopenia, resource constraint settings, ITP, chronic ITP, immunosuppresents

Introduction

Immune thrombocytopenia (ITP) is a benign hematological disorder characterized by low platelet counts in peripheral blood with or without bleeding manifestations [1, 2]. It is one of the commonest reasons for seeking consultation in hematology clinics [3]. Although low

platelet count is considered as a risk factor for bleeding, all ITP patients with thrombocytopenia do not bleed [4-6]. The diagnosis is established by the exclusion of secondary causes of thrombocytopenia [1, 7]. Corticoteroids are the first-line therapy with a good overall response rate (50-80%) [8]. However, steroid dependency or relapse after initial treatment with corticosteroids is common. Also, long term use of steroids has its own side effects like osteoporosis, uncontrolled sugars, and hormonal imbalance. Therefore, a second-line agent is required in 30-80% of cases of ITP [9].

Thrombopoietin receptor agonists (TPOs), rituximab, and splenectomy are the preferred second-line agents after first line failure [9-11]. Azathioprine, danazol, dapsone, vincristine are also used as a second-line agents but with limited efficacy [10]. The decision to choose a second-line agent is primarily based on the patient's preference for high efficacy, fixed-dose therapy, and preference of medical versus surgical intervention [11]. However, in developing countries, financial capabilities and availability of drugs may at times play a major role in decision making for the choice of second-line therapy in ITP [9, 11].

As an immunosuppressant, azathioprine has been used for more than half-a-century. It is a cost effective and readily available drug in most of the developing countries [12]. There have been reports on efficacy and safety of azathirpoprine in ITP. However, due to limited data on the efficacy and safety of azathioprine, it is seldom used in ITP. We aimed to study the efficacy and long-term safety profile of ITP patients treated with azathioprine.

Methods

Patients

This was a retrospective, single-center study conducted at a tertiary care hospital in Northern India. The study was approved by the Institutional Review Board (IEC75/2020). Medical treatment details were accessed from the outpatient clinic files, and inpatient hospital admission and discharge notes. Relevant data were entered in the pre-defined password-protected excel sheet. Being a retrospective study, the missing data were minimized by contacting patients or their family members through phone calls and WhatsApp. The patients were diagnosed as per the International Working Group Criteria (IWG criteria) [13]. ITP patients who had received at least one line of therapy before receiving azathioprine were included in this study. An informed written consent was taken from the patients or guardian of the patients'. Patients with missing follow-up information and who denied giving consent were excluded from the study. Patients on concomitant drugs for ITP and secondary ITP were also excluded from the study.

Treatment with azathioprine

Before the treatment with azathioprine, patients were explained regarding the possible adverse effects of the drug. All patients received oral azathioprine at starting dose of 1 mg/kg/day (50 mg or 100 mg tablets were used) once daily, which was gradually increased up to a maximum of 2 mg/kg/day, depending upon platelet response and tolerability. Complete blood count (CBC) and liver function test (LFT) was monitored regularly during the therapy.

Efficacy and safety profile

Demographic profile of the patient was recorded along with ITP diagnosis date and the prior therapies received. The dose of azathioprine, any modification and the duration were recorded. The reason for discontinuation was recorded. The primary end point was overall response (ORR). Adverse events were recorded and graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [14].

Definitions for the study [1, 13]

Partial response (PR) was defined as a platelet count of ≥30,000/μL or double from the baseline, with no active bleeding manifestations. Complete response (CR) was defined as a platelet count of ≥100,000/μL with no active bleeding manifestations.

Overall response rate (ORR) was defined as proportion of patients achieving CR or PR. No response was defined as a platelet count <30,000/μL or < double from the baseline, or having active bleeding manifestations requiring another line of therapy. Relapse was defined as

Table 1. Demographic profile and baseline clinical characteristics of ITP patients who received azathioprine

Variable	n (%)
Evaluable patients	63
Females	29 (46.03%)
Age (years), median (range)	28 (15-68)
Interval from ITP diagnosis to azathioprine (days), median (IQR)[#]	539 (323-980.5)
Number of prior therapies, median (Range)	3 (1-6)
One line	9 (14.3%)
Two lines	13 (20.6%)
Three lines	16 (25.4%)
Four lines	13 (20.6%)
Five lines	8 (12.7%)
Six lines	4 (6.3%)
Different therapies received prior to azathioprine	
Corticosteroid	58 (92%)
Immunoglobulin	24 (38%)
Anti-RhD Immunoglobulin	5 (7.9%)
Rituximab	16 (25.4%)
Splenectomy	6 (9.5%)
Eltrombopag	6 (9.5%)
Dapsone	47 (74.6%)
Danazole	25 (39.7%)
Vincristine	12 (19%)
Baseline Hemoglobin (g/dL), mean (SD)[*]	12.64 (2.11)
Baseline WBC (/μL), median (IQR)	9400 (7900-10500)
Baseline Platelet count (/μL), median (IQR)	10000 (8000-15000)

[#]IQR: interquartile range; [*]SD: standard deviation.

any new-onset bleeding manifestation necessitating therapy or drop in platelet counts below 30,000/μL or patients who were started on another line of therapy or underwent splenectomy for low platelet counts after achieving response on Azathioprine. Response duration was defined as time duration from the day of starting azathioprine to the day of documented relapse.

Statistical methods

The information was collected in Microsoft Excel (R) and was analysed using statsmodels package (ver 0.11) in Python 3.7 and survival package [15, 16]. A Package for Survival Analysis in S. version 2.38, in R 3.5.1 [17]. Baseline variables were summarised using standard summarisation measures.

A timeline was made for each patient with entry time being the time when azathioprine was started. Baseline characteristics were noted for each patient. Dose of azathioprine was entered as time varying covariate. Each patient would start in a state with disease (state 0), and then would transit into one of the following states: no disease (CR/PR) (state 1) and death (state 2). From this dataset, Kaplan Meier analysis and Cox proportional hazards regression analysis were performed to assess overall remission (state 0->1), relapse (state 1->0) and overall survival (0, 1->2). For analysis of complete remission, the timeline was subdivided into the following states: disease presents (state 0), PR (state 1), CR (state 2) and death (state 3) and the same above techniques were used to analyse it. To assess the significance of different variables, 95% confidence interval and *P* value <0.05 were used.

Results

Demographics and baseline laboratory parameters

A total of 347 ITP patients were managed at our institute from 2012 to 2019. Seventy-nine

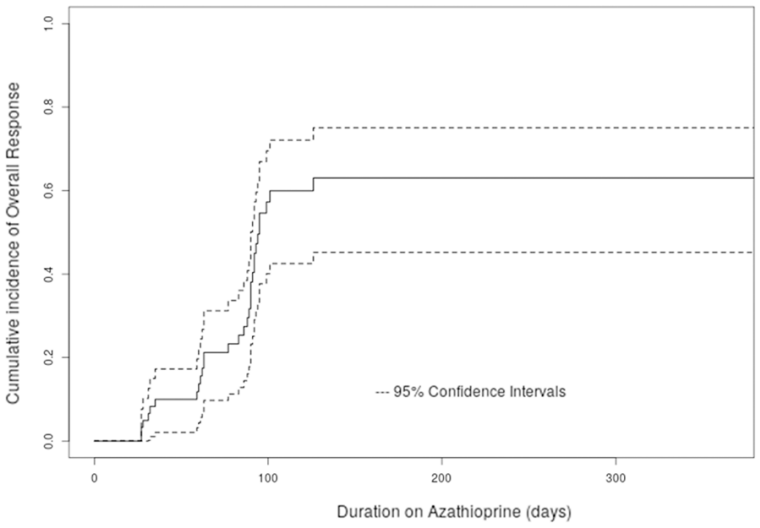

Figure 1. The figure shows the cumulative incidence of overall response with duration on azathioprine (in days).

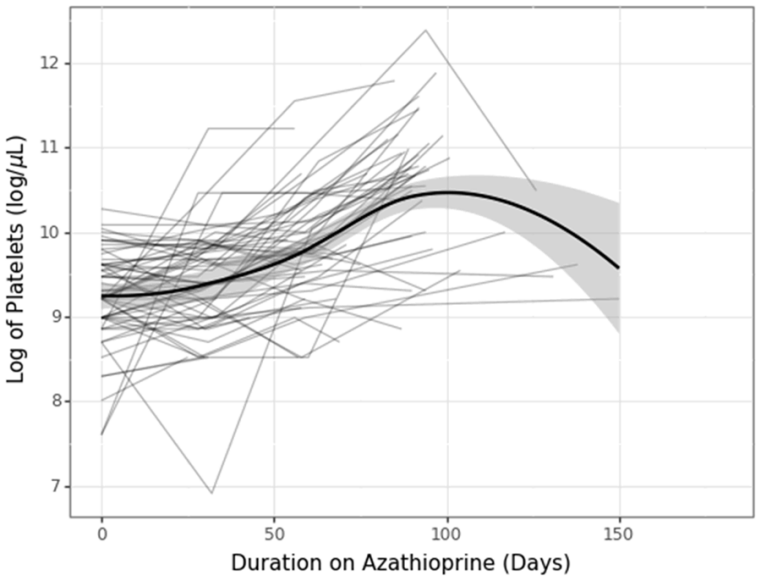

Figure 2. The figure shows the kinetics of log of platelets (/microL) with duration on azathioprine (in days), till 150 days. The thick line depicts the LOESS fit with the shaded area being the 95% CI. The light lines depict kinetics of platelets in individual patients.

patients received azathioprine during this period. After screening for inclusion and exclusion criteria, the treatment outcomes of 63 patients were analyzed. Eleven patients had no entry in the respective file after start of therapy and could not be contacted on telephone. Therefore, their disease status couldn't be ascertained and were excluded from the study due to loss of follow up (1.37 loss to follow up/year). Two patients had concomitant drugs for ITP (steroid 2, dapsone 1), two had secondary ITP and one patient refused to give consent. The baseline demographic characteristics and pre-azathioprine parameters are summarised in **Table 1**.

The median age of our study population was 28 years (range 15-68); 29/63 patients (46.03%) were females. ITP patients who had received azathioprine after at least one prior line of treatment were included in the study. The median duration from diagnosis to azathioprine was 539 days (323 days-980.5 days). Patients included in this study had received a median of 3 (range 1-6) prior lines of therapies; 38/63 patients (60.32%) had received ≥3 prior therapies. Six patients (9.5%) had relapsed after splenectomy, and 16 patients (25.4%) had relapsed after rituximab therapy. The mean baseline hemoglobin, white blood cells (WBCs), and platelets were 12.64 g/dL, 9400/μL, and 10000/μL, respectively.

Response rate

The median time to response was 95 days (90 days-not reached) and the cumulative overall response rate (complete and partial response) at day 30, day 60, and day 90 were 4.9%, 13.7%, and 38.1%, respectively (**Figures 1**, **2** and **Table 2**). Only one patient achieved a complete response with azathioprine in our study.

Factors affecting the response to azathioprine

On univariate analysis, there was no effect of age, sex, duration of disease, prior lines of therapy received, and platelet count on the overall response to Azathioprine in our study population (**Table 3**).

Table 2. Response to azathioprine in ITP patients

Variable	n (%) or median (range)	95% CIs
Time to response (days), median	95	90-not reached
Cumulative incidence of overall response		
At day 30 of Azathioprine	3 (4.9%)	0-10.2%
At day 60 of Azathioprine	8 (13.7%)	4.4-22.1%
At day 90 of Azathioprine	20 (38.1%)	23.2-55.1 %
Patients achieving complete response		
At day 30 of Azathioprine	0 (0)	-
At day 60 of Azathioprine	1 (1.8%)	0-5.3%
At day 90 of Azathioprine	1 (1.8%)	0-5.3%
Follow up (years), median (IQR)	5.7 (4.5-7.9)	
Time to relapse in years, median	7	6.04-not reached
Cumulative incidence of relapse		
At 1 year	0	Not applicable
At 2 years	2 (6.9%)	0-15.7%
At 3 years	4 (14.1%)	0.3-25.9%
At 5 years	6 (21.2%)	4.6-35%

Table 3. Univariate analysis for response assessment at day +30 and day +90 after azathioprine

	Hazard ratio	P	30 days expected events (SE)	90 days expected events (SE)
Age (per decade)	1.05	0.767		
23 year			0.048 (0.006)	0.455 (0.061)
38 year			0.052 (0.005)	0.486 (0.046)
Sex	0.75	0.44		
Male			0.043 (0.007)	0.414 (0.069)
Female			0.058 (0.012)	0.552 (0.112)
Duration of ITP (years)	0.898 (per 1 log year)	0.569		
1 year			0.052 (0.004)	0.495 (0.039)
3 year			0.046 (0.008)	0.439 (0.073)
Prior therapy	0.929	0.84		
≤3 prior lines of therapy			0.051 (0.008)	0.488 (0.072)
>3 prior lines of therapy			0.048 (0.011)	0.454 (0.108)
Hemoglobin (g/dL)	1.102	0.301		
11			0.044 (0.009)	0.44 (0.096)
14			0.059 (0.008)	0.6 (0.056)
WBC (/microL)	0.944 (per 1000 WBC/microL)	0.347		
7900			0.04 (0.003)	0.533 (0.042)
10400			0.035 (0.002)	0.463 (0.023)
Paltelets	0.965 (per 1000 platelets/microL)	0.326		
8000			0.056 (0.006)	0.557 (0.059)
15000			0.044 (0.003)	0.436 (0.044)

Response evaluation at follow up

Only one patient had a significant (WHO bleeding scale ≥3) bleeding episode, in the form of subdural hematoma, in the study population necessitating platelet transfusion and rescue therapy. There were a total of 13 bleeding episodes during the follow-up, and all were WHO grade 1.

A total of six patients on azathioprine relapsed during follow-up. The cumulative rate of relapse

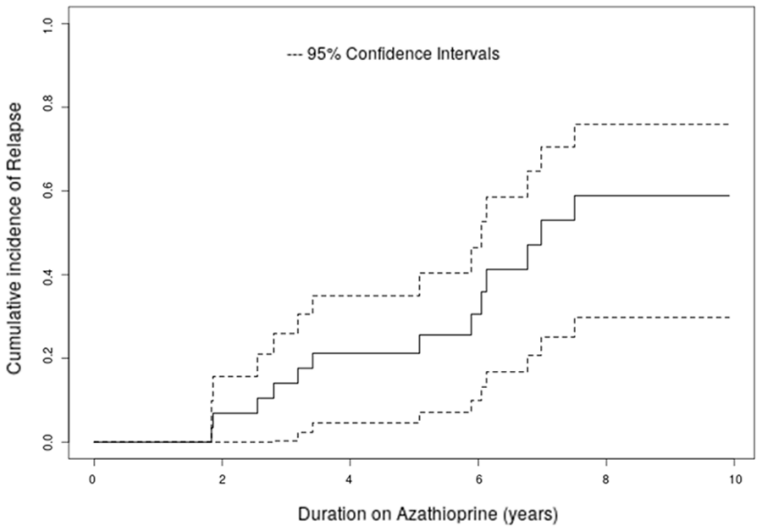

Figure 3. The figure shows the cumulative incidence of relapse with duration on azathioprine (in years).

at two years, three years, and five years were 6.9%, 14.1%, and 21.2%, respectively. There was no significant difference in the outcomes (response rate or relapse) among the subgroups based on age, sex, duration of disease, lines of prior therapies, or baseline platelet count (**Figure 3**; **Table 4**).

A total of 26 patients stopped azathioprine after they achieved some response (CR/PR). The median duration of azathioprine intake in these patients was 1067.5 days (range: 236 days-2465 days). Subsequently, they remained under follow up for a median of 870 days (range: 392 days-1928 days), and twelve of them relapsed.

Side effects of azathioprine therapy

Twenty-six patients (26/63, 41.27%) reported one or more adverse events while being on azathioprine therapy. A total of 30 adverse events were noted. Leucopenia was the most frequent adverse event followed by anemia and hepatobiliary laboratory dysfunction as measured by deranged aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Serious adverse events (grade ≥3 CTCAEv4) were noted in only three patients. One patient had severe sepsis and he succumbed due to multiorgan dysfunction, while the other two had severe neutropenia (grade 4), which resolved after temporary cessation of azathioprine (**Table 5**).

Discussions

ITP is a heterogeneous disease with relapsing-remitting course and various drugs are used for its treatment. Availability of drug and cost of treatment are the two important parameters that determine the use of ITP-specific drugs in a developing country like India. Azathioprine is an affordable and easily available drug with good efficacy and safety profile in other autoimmune diseases. Therefore, it has the potential to be an alternative to various other drugs used in the treatment of ITP in developing countries [12]. Azathioprine is also considered safe during pregnancy and for lactating mothers [8, 18]. In our study, the cumulative incidence of overall response to azathioprine at day 90 was 38.1%, which is inferior to overall response rate of 54%-75% in previously published studies [8, 12, 19-23]. The studies with highest response rate were reported from China and Nepal (71.4% and 75% respectively). They used azathioprine as second line therapy after steroid (single line), and that may be the reason for superior response [12, 20]. The complete response rate of 1.8% in our study is lesser in comparison to 16%-38% CR rate in previous studies [12, 19] (**Table 6**). We believe that this inferior response in our study, may be due to a lower starting dose of azathioprine, longer duration between ITP diagnosis and start of azathioprine, and multiple lines of therapy prior to start of azathioprine in our study population.

On univariate analysis, the response to azathioprine was not significantly affected by factors like age, sex, duration of ITP, prior lines of therapy, and baseline hematological parameters (hemoglobin, WBC, platelet count). This finding is in agreement with the previously published studies [12, 19, 20].

On follow-up of patients who responded to azathioprine therapy, only six patients relapsed after five years of therapy (cumulative incidence of relapse at 5 years 21.2%). The relapse

Table 4. Univariate analysis for relapse assessment at 1 year and 3 year after azathioprine

	Hazard ratio	P	2-year expected events (SE)	5-year expected events (SE)
Age (per decade)	0.836	0.534		
21 yr			0.082 (0.015)	0.273 (0.062)
38 yr			0.061 (0.018)	0.202 (0.067)
Sex	1.614	0.404		
Male			0.086 (0.024)	0.286 (0.05)
Female			0.053 (0.015)	0.177 (0.083)
Duration of ITP (years)	1.875 (per 1 log year)	0.085		
1 year			0.054 (0.004)	0.182 (0.011)
3 year			0.107 (0.09)	0.364 (0.022)
Prior therapy	2.036	0.207		
≤3 prior lines of therapy			0.05 (0.012)	0.169 (0.041)
>3 prior lines of therapy			0.102 (0.016)	0.346 (0.055)
Hemoglobin	0.88	0.403		
11			0.086 (0.013)	0.288 (0.065)
14			0.057 (0.014)	0.191 (0.049)
WBC	0.872 (per 1000 WBC/microL)	0.15		
7000			0.099 (0.011)	0.341 (0.108)
11800			0.051 (0.024)	0.177 (0.081)
Paltelets	1.009 (per 1000 platelets/microL)	0.841		
6000			0.066 (0.018)	0.221 (0.061)
15000			0.072 (0.013)	0.239 (0.039)

Table 5. Adverse events noted with azathioprine therapy

	Total Events	Grade ≥3
Anemia	7	0
Leucopenia	14	2*
Increased AST/ALT**	3	0
Increased Bilirubin	0	0
Sepsis	2	1#
Headache	1	0
Nausea/vomiting	3	0
	30	3

*All recovered with temporary cessation of azathioprine. **AST: aspartate aminotransferase; ALT: alanine aminotransferase. #One pateint died due to severe sepsis and multi-organ failure, had diabetes mellitus as comorbidity.

rate in our study was lower than 50%-70% relapse rate in the published studies [19, 20]. On univariate analysis, factors like age, sex, duration of ITP, prior lines of therapies, and baseline hematological parameters did not affect the relapse rate, which is in congruence with the previously published data [19, 20].

Azathioprine was stopped in 26 patients who had responded (CR/PR). Six out of 26 patients (23.08%) relapsed after a median follow-up of 870 days (range: 392 days-1928 days). The treatment-free survival after azathioprine has been reported to be 10-40% in previous studies [19, 24]. Therefore, our result is superior and promising for the future.

Azathioprine causes bone marrow suppression, a decrease in lymphocytes, reduced immunoglobulin production, and a decrease in interleukin 2 (IL-2) secretions. Therefore, anemia, leucopenia, and increased susceptibility to infections are the common adverse events associated with it [25-28].

In our study, leucopenia was the commonest adverse event (14/63, 22.22%). However, all patients recovered with either temporary cessation of azathioprine or dose reduction. This incidence was comparable to 15-20% incidence of leucopenia in a previous study [19, 20]. One patient died due to sepsis and multi-organ dysfunction while being on azathioprine, in spite of achieving a platelet count of >50000/μL earlier with treatment. Apart from ITP, this patient also had uncontrolled diabetes mellitus. Hence, multiple factors could have

Table 6. Comparison of results of index study with the previously published studies on azathioprine as second-line therapy in ITP

Study	Quiquandon et al. 1990 [19]	Poudyal et al. 2016 [12]	Chang et al. 2018 [20]	Depré et al. 2018 [21]	Present study
Stydy design	Retrospective	Prospective	Retrospective	Retrospective	Retrospective
Number of pts (N)	53	24	57	90	63
Median age, years (range)	54 (17-89)	Mean: 39 years	51 (19-81)	Mean: 50.5 years	26 (15-68)
Women	37 (69.81%)	17 (70.8%)	46 (80.7%)	-	29 (46.03%)
Duration of ITP (month)	19 (6-350)	22 days	18.7 (31-193)	-	539 days (323-980.5)
Prior lines of therapy	≥1	1	1	-	3 (1-6)
Splenectomy	40 (75.47%)	Nil	-	-	6 (9.5%)
Rituximab	Nil	Nil	-	-	16 (25.4%)
Baseline Platelet count (mean)/μL	<50,000	8958.33	23500	-	10000
Starting dose of Azathioprine	150 mg OD	2 mg/kg/day	100-150 mg/day	1-2 mg/kg/day	1-2 mg/kg/day
Concomitant drugs	Prednisolone (n=10)	Nil	Nil	Prednisolone (n=78)	Prednisolone (n=6) Danazole (n=5)
Overall response	34 (64.15%)	18 (75%)	41(71.4%)	49 (54%)	Cumulative ORR at day 90: 38.1%
Median time to response	4 months	-	-	-	95 days
Follow up duration, Median	6 years	-	39 (6-110) months	-	5.7 years (4.5-7.9)
Sustained response	At 1 year: 21 (40%) At 2 year: 17 (32%)	-	At 3 year 44%	-	Cumulative sustained response rate at five years: 78.8%
All ADRs[#]	9 (16.98%)	6 (25%)	19 (33.33%)	20 (22.22%)	26 (41.27%)
ADRs ≥gd3	Nil	Nil	1 (1.75%)	-	3 (4.76%)

[#]Adverse drug reaction.

contributed to his demise. Being a purine antimetabolite, azathioprine is known to be associated with increased risk of malignancy. However, there was no incidence of malignancy in our study group and many other published studies on azathioprine in ITP [27, 28]. However, longer follow-up shall be required to ascertain the risk of malignancy with azathioprine, as malignancy can be seen decades after azathioprine exposure.

Our single-centre retrospective study has a small sample size but it is one of the largest studies on azathioprine in ITP. The patients included in our study had a fairly long follow-up duration. We tried to minimise the missing data through phone calls. Pre-treatment genotyping for thiopurine S-methyltransferase (TPMT) and nucleotide diphosphate 15 (NUDT15) is helpful in the identification of IBD patients at increased risk for azathioprine toxicity. Adoption of a similar genotype-based approach might reduce the incidence of azathioprine-related myelosuppression in ITP patients as well. Unfortunately, the genotyping for TPMT and NUDT15 couldn't be performed in our patients due to logistic constraints.

Overall, azathioprine has a good response rate in chronic ITP. It is well-tolerated with minimal and manageable side effects. Prospective studies may provide more robust data on the use of this cheap and easily available drug for patients living in resource constraint settings.

Disclosure of conflict of interest

None.

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