Indian J Hematol Blood Transfus (Jan-Mar 2019) 35(1):176–178
https://doi.org/10.1007/s12288-018-1012-3

CORRESPONDENCE

6-Mercaptopurine Fails to Improve Platelet Count in Pediatric Chronic Immune Thrombocytopenia

Anirban Das[1] · Prateek Bhatia[1] · Amita Trehan[1]

Received: 4 June 2018 / Accepted: 31 August 2018 / Published online: 8 September 2018

Dear Editor,

Majority of children with chronic immune thrombocytopenia (ITP) have a benign course. Disease-modifying therapy using dexamethasone, rituximab, TPO-agonists, or splenectomy, each with long-term adverse effects and financial implications, is restricted for those with significant or troublesome bleeds [1, 2]. The index study aimed to evaluate response to 6-mercaptopurine (6MP) in children with chronic ITP, based on previous report of successful use [3]. Successive children with chronic ITP having: (a) recurrent, troublesome skin/subcutaneous/mucosal bleeds (grade 2/3), (b) no sustained response to corticosteroids, and, (c) negative HIV and ANA titers, were enrolled between July and December 2010, and prospectively started on 6MP at a dose of 50 mg/m2/day for 4-months. Pre-treatment platelet counts were compared to counts at 1, 2, 3, 4 and 6-months after staring 6MP. Complete response was defined as an increase to $> 100 \times 10^9$/L, and a clinically relevant response as increase to $> 30 \times 10^9$/L with twofold increase from baseline and absence of bleeding [4]. Physician-determined reduction in severity and frequency of bleeds, parental perception on improvement in quality of life, breakthrough bleeding warranting additional therapy, and significant adverse events were recorded. Repeated measure ANOVA was used to analyze change in the platelet counts with time (SPSSv20).

Eight children were enrolled (Table 1). Median duration of thrombocytopenia prior to initiating 6MP was 3.2-years. Median platelet count was 4×10^9/L (IQR: 2;6). Serial counts demonstrated that no patient achieved complete response (Table 1). Clinically relevant response was seen in 2/8 (25%) patients at 1 and 2-months with increase in platelet count to 92×10^9/L and 53×10^9/L, respectively. However, counts for both decreased within a month while on treatment. Overall, there was no significant increase in platelet counts at 1, 2, 3, 4 or 6-months ($p = 0.42$). There was a transient reduction in the clinical severity of bleeds and improvement in quality of life in 3/8 (37.5%) children, 1-month following initiation of 6-MP, only one of whom had an increase in counts to 92×10^9/L. Significant bleeding (grade 4) while on 6MP was documented in 3/8 (37.5%) children, warranting additional treatment. No significant adverse event was reported other than reversible, asymptomatic leucopenia in 1/8 (12.5%).

The purine metabolites 6MP and azathioprine have immunosuppressive effects on B and T-lymphocytes. Given the rarity of serious bleeds in chronic ITP, the latter itself being uncommon in children, prospective studies on the use of 6MP have been performed in small cohorts and are infrequently reported. Sobota et al. [3] had reported response in 85% children with chronic ITP with a mean increase of 162×10^9/L, time to response of 2.7 ± 1.5-months, duration of response of 16-months, and continued disease remission after stopping therapy in 12.5%. Azathioprine is a related agent which is slowly but completely metabolized to 6MP and is supposed to have a better safety profile. It has been documented to produce response-rates between 51 and 87% in adults, and 80% in a small series of 5 children [5].

✉ Amita Trehan
trehanamita@hotmail.com; trehan.amita@pgimer.edu.in; amita911@gmail.com

[1] Paediatric Haematology/Oncology Unit, Department of Paediatrics, Advanced Paediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Table 1 Clinical characteristics of 8 children with chronic ITP on 6-mercaptopurine

No.	Age (years)	Sex	Duration of thrombocytopenia (years)	Past treatments	Response to past treatments	Indication	Grade of hemorrhage	Platelet count at baseline ($\times 10^9$/L)	Serial platelet counts on serial follow-up ($\times 10^9$/L)	Course on treatment	Grade of hemorrhage	Additional treatment needed
1	11	Male	8	Prednisone	Partial response to the first course, subsequently refractory	Recurrent bruising	2	4	2, 53, 1, 21, 6	Petechiae, occasional epistaxis	3	None
2	12		Female	4								

Methylpredisolone, oral predmisone None Epistaxis, petechiae 2 2, 22, 1, 5, 5 Menorrhagia 4 Tranexemic acid, prednisolone 3 Male 4 Prednisone None Recurrent skin bleeds 2 1, 2, 1, 5 Severe gastro-intestinal bleed 4 Methylprednisolone 5 Male 0.67 Methylprednisolone, dapsone, azathioprine Partial response to methylprednisole and dapsone at first administrations; subsequently refractory Recurrent skin bleeds 2 3, 1, 4, 5 Skin bleeds None 6 Male 4 Prednisone None Recurrent bruising 1 6, 3, 29, 24, 6 Skin bleeds, leucopenia None 7 Female 2.5 Prednisone None Large palpable ecchymosis, recurrent oral mucosal bleed 2 1, 3, 19, 3, 4 Skin bleeds and epistaxis None 8 Female 0.5 Methylprednisolone None Recurrent skin bleeds and epistaxis 3 10, 4, 10, 1 Significant epistaxis 4 Oral prednisolone, tranexamic acid, nasal packing Male 1.5 Prednisone None Recurrent large hematomas on forehead 2 15, 5, 5, 1 Petechia and subcutaneous hematoma 3 None

The lack of response to purine metabolite in our study can be explained by two possible reasons. Firstly, the duration of thrombocytopenia prior to initiation of 6MP was prolonged in the index study (3.2-years, vs 18.7-months in the study by Sobota et al. [3]). Early suppression of the underlying autoimmune mechanism could have provided a benefit in the previous study. However spontaneous remissions, and a waxing and waning course are well known in chronic ITP, and previous reports of response could have been merely fortuitous.

In conclusion, despite small numbers, the total lack of response to 6MP in children with chronic ITP in the current study was disheartening. Larger prospective studies would need multi-center collaboration and are indicated to confirm or refute the efficacy of 6MP in chronic ITP.

Author's Contributions AT: planned the study. AD: collected and analysed the data, and prepared the manuscript. PB: reported the hematology.

Compliance with Ethical Standards

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

Ethical approval Ethical approval was duly obtained for this study.

Informed consent Informed consent was duly obtained for this study.

References

1. Neunert C, Lim W, Crowther M, American Society of Hematology et al (2011) The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 117:4190–4207
2. Neunert CE, Buchanan GR, Imbach P, Intercontinental Cooperative ITP Study Group Registry II Participants et al (2013) Bleeding manifestations and management of children with persistent and chronic immune thrombocytopenia: data from the Intercontinental Cooperative ITP Study Group (ICIS). Blood 121:4457–4462
3. Sobota A, Neufeld EJ, Lapsia S et al (2009) Response to mercaptopurine for refractory autoimmune cytopenias in children. Pediatr Blood Cancer 52:80–84
4. Rodeghiero F, Stasi R, Gernsheimer T et al (2009) Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 113:2386–2393
5. Hilgartner MW, Lanzkowsky P, Smith CH (1970) The use of azathioprine in refractory idiopathic thrombocytopenic purpura in children. Acta Paediatr Scand 59:409–415