A Possible Second Line Drug in Chronic Steroid Refractory ITP: A Tertiary Care Experience

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***Abstract*-** ITP is a common acquired autoimmune disorder defined by a low platelet count secondary to accelerated platelet destruction or impaired thrombopoiesis by antiplatelet antibodies. **Aim**: we aimed to assess the possible role of vincristine as second line drug in chronic steroid refractory ITP. **Methods**: The study was conducted in a tertiary care hospital and included all adult patients (n=50) diagnosed as ITP who were previously treated unsuccessfully with steroids. All patients received four doses of vcr 1.5 mg/m^2/wk for four consecutive weeks. This was followed by observing plt count on day 1, 3 & 7 for four consecutive weeks. **Results:** This study showed that out of all patients enrolled for this study 80% were females (n=40) and 20% were males (n=10). Among all female patients (n=40) 4%(n=2) showed no response, 58% (n=29) were partial responders and 18% (n=9) showed complete response. We had 10 male patients out of which 18% (n=9) showed partial response and 2%(n=1) showed complete response. Overall 4%(n=2) patients showed no response, 76%(n=38) showed partial response and 20%(n=10) showed complete response. Total number of patients which showed some response to VCR including both partial and complete response was seen in 96% (48) which is significantly high and statistically significant ($_p$value≤0.0001).The average plt count before VCR was 4 and peak plt count achieved on an average was 79.2.**Conclusion;** vcr has a double advantage (cytostatic and thrombopoetic) that would be an advantage in ITP patients. Duration of response and relapse rate needs further studies.

***Index Terms*-** Idiopathic thrombocytopenic purpura (ITP), vincristine (VCR), platelet (PLT), Steroids.

I. INTRODUCTION

Immune (autoimmune, idiopathic) thrombocytopenic purpura (ITP) is a common acquired autoimmune disorder defined by a low platelet count secondary to accelerated platelet destruction or impaired thrombopoiesis by antiplatelet antibodies. The diagnosis of ITP requires decreased platelets on the blood film and the exclusion of other causes of thrombocytopenia. Normal or increased numbers of marrow megakaryocytes are found in the majority of patients. [1]ITP is usually classified based on the absence or presence of underlying diseases (primary or secondary), age (adult or childhood ITP), and duration of the disease (acute, persistent or chronic)[2].

Incidence: The reported annual incidence of ITP is 5.5 per 100,000 persons when defined by a platelet count of less than 100 x 10^9/L and 3.2 per 100,000 using a cutoff platelet count less than 50 x 10^9/l [3]. The estimated female-to-male ratio was 1.7.[3-4]

Clinical features: ITP usually is a chronic disease in adults. Chronic ITP is traditionally defined as ITP with a platelet count less than 150 x 10^9/L for more than 6 months without other cause. [5]A large number of patients are diagnosed incidentally in routine complete blood counts. Symptoms and signs of ITP depend on the platelet count. Approximately one-third of patients have platelet counts greater than 30 x 10^9/L at diagnosis and no significant bleeding. [5] In majority of patients symptoms of bleeding are generally seen in patients with counts below this level. Ecchymoses ,petechiae, epistaxis, menorrhagia, and gingival bleeding are common. Hematuria, hemoptysis, and gastrointestinal bleeding are less common. Intracerebral bleeding is rare and usually occurs in patients with platelet counts less than 10 x 10^9/L . The incidence of life-threatening complications is highest in patients older than 60 years, but,mortality rates are low in patients with ITP, even in presence of severe thrombocytopenia. [5-8]

Laboratory features:

Platelet Counts and Size: Thrombocytopenia is defined as a blood platelet count less than 150 x 10^9/L. The blood film usually demonstrates isolated thrombocytopenia without erythrocyte or leukocyte abnormalities. Platelet anisocytosis is a common finding in ITP. Mean platelet volume and platelet distribution width are increased. Platelets may be abnormally large or abnormally small. The former reflect accelerated platelet production, [9] and the latter platelet microparticles reflect platelet destruction.[10] The observation of giant platelets should trigger consideration of inherited platelet disorders, which often are misdiagnosed as ITP.[11] Bleeding time correlates inversely with platelet count if the count is less than 100 x 10^9/L, but may be normal in patients with mild or moderate thrombocytopenia. [12]The ultrastructure of ITP platelets viewed by electron microscopy is similar to that of normal platelets.[13]

Autoimmune hemolytic anemia with a positive direct antiglobulin (Coombs) test and reticulocytosis may accompany ITP; this association is termed *Evans syndrome*.[14] The latter syndrome can include immune neutropenia[15].Neithererythrocyte poikilocytosis nor schistocytes should be present.[15]

Marrow examination: It is not always required to make a diagnosis of ITP in adults, generally reveals normal or increased numbers of megakaryocytes of normal morphology, although a decreased number of megakaryocytes does not rule out ITP.[16]

Therapy, Course, and Prognosis: Whatever little is known of the natural course of moderate or severe ITP derives from

before the glucocorticoid era, and suggests that left untreated, ITP in adults typically is a chronic disease, with infrequent spontaneous remissions, in contrast to ITP in children. Even with glucocorticoid therapy, complete remission usually is not seen.[6] The risk of hemorrhagic complications is greater in patients older than age 60 years. [3]ITP may respond to various agents or manipulations, including glucocorticoids, splenectomy, IVIg, anti-(Rh)D, danazol, and antineoplastic drugs such as vincristine and azathioprine. Thus, the patient's symptoms and initial response to therapy should dictate ongoing therapy.[17]

Initial Management: Because most ITP patients are diagnosed incidentally in routine evaluation, signs and symptoms of bleeding are important in determining whether any treatment is required. Patients with no bleeding and consistent platelet counts in excess of 50 x 10^9/L do not require treatment and can be observed periodically. These patients are at low risk for clinically important bleeding and may safely undergo invasive procedures.[6,7,17] Patients with platelet counts between 30 and 50 x 10^9/L generally do not experience clinically important bleeding but may manifest easy bruising. They usually do not require treatment. Careful followup is necessary for these patients because the clinical course is difficult to predict. Simple observation is not recommended for patients with platelet counts less than 10 x 10^9/L, in those with platelet counts between 10 and 50 x 10^9/L and significant mucosal bleeding, or in those with risk factors for bleeding, such as uncontrolled hypertension, peptic ulcer, or a vigorous lifestyle.[16] Emergent treatment should be instituted in patients with intracranial or gastrointestinal bleeding, massive hematuria, internal hematoma, or in need of emergent surgical intervention. The presence of extensive purpura or hemorrhagic bullae in mucosal tissues is a harbinger of life-threatening bleeding and warrants therapy. Patients with any of these findings should be hospitalized and monitored closely. High-dose parenteral glucocorticoid therapy (methylprednisolone 1 g/day in divided doses for 1–3 days), IVIg (1 g/kg per day for 2 days), or IVIg and parenteral glucocorticoids in combination are generally recommended for those patients.[1] In most patients, IVIg increases the platelet count within 2 to 3 days.[1,17,6}

II. Aims and Objectives

To evaluate the practical role of vinca alkaloids as second line drug in idiopathic thrombocytopenic purpura in our population.

III. Material and Methods

This study was conducted in Department of Medicine and Clinical Hematology in Sheri Kashmir Institute of Medical Sciences, Jammu and Kashmir. Our study was a prospective study.

Inclusion criteria: 1. Subjects with relapsed or refractory ITP. (Refractory = no response after six weeks of oral prednisolone and /or three doses of pulse therapy with methylprednisolone1gram, relapse = completed 6 weeks course of steroids with loss of response). **2**. Written informed consent.

Exclusion criteria: 1. Persons who have under gone spleenectomy for idiopathic thrombocytopenic Purpura. **2**. Uncontrolled co-morbidities such as malignancy or other confounding diseases. **3**. Use of anticoagulants or chemotherapy or known other disorders and/or treatments influencing the platelet number within 3 months of randomization date (tranexaminic acid treatment is allowed). **4**. Pregnant or lactating females. **5**. Systemic infections: active viral infections, including HIV,HCV infections. **6**. Systemic autoimmune disorders e.g. Systemic lupus erythematosus (SLE).

Statistical methods: Statistical package for social sciences (SPSS) version 20 was used for statistical analysis. Standard statistical methods were used and tests like T test for normally distributed continuous variables and the Pearson chi square test. Anova was used for comparison of more than two variables. A p value< 0.05 was considered statistically significant.

Criteria of response: Criteria for response are defined as follows: **1.** Complete response; (normal platelet count $\geq 100_{\times}10^9$/l measured on two occasions>7days apart and disappearance of signs of bleeding). **2.** Partial Response; A platelet count of $30_{\times}10^9$/l to 100×10^9/l on two occasions >7days apart and absence of signs of bleeding. **3.** No response; A platelet count $<30_{\times}10^9$/l or presence of bleeding [24]

IV. Results

This study was conducted from august 2012 to November 2014 in our tertiary care hospital. The total number of patients enrolled in this study was 50 which included diagnosed cases of ITP both males and females above ten years of age. Among this 40 were females and 10 were males. The age and sex distribution is shown in table 1 figure 1, 2.

Figure 1: Age distribution

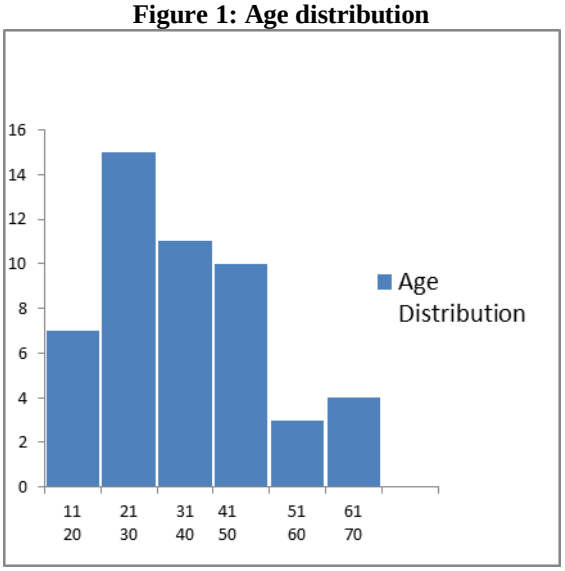
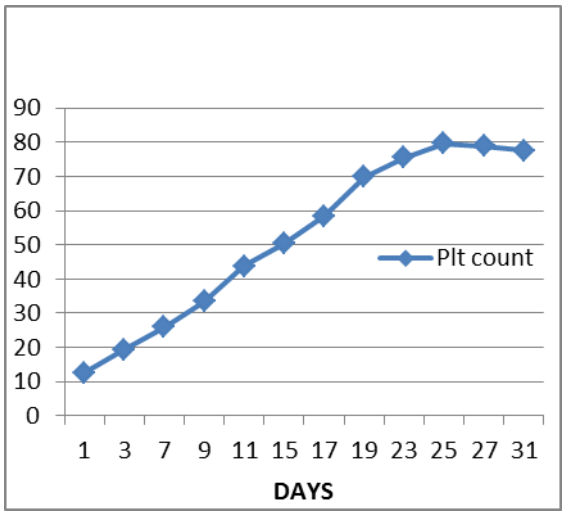


Table 1: Age distribution.

AGE	MALE	FEMALE	TOTAL
11 to 20	1	6	7
21 to 30	1	14	15
31 to 40	0	11	11
41 to 50	5	5	10
51 to 60	0	3	3
61 to 70	3	1	4
Total	10	40	50

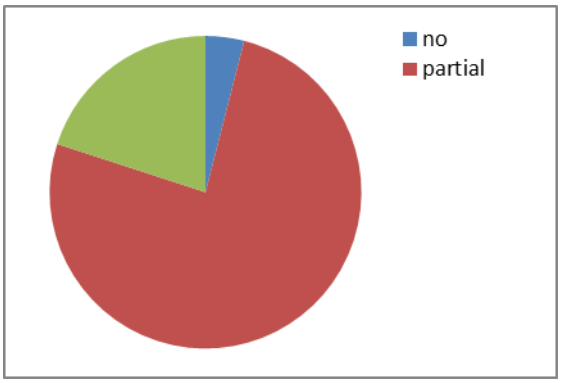
Platelet response: The results are shown in figure 2, 3.

Figure 2: Platelet response



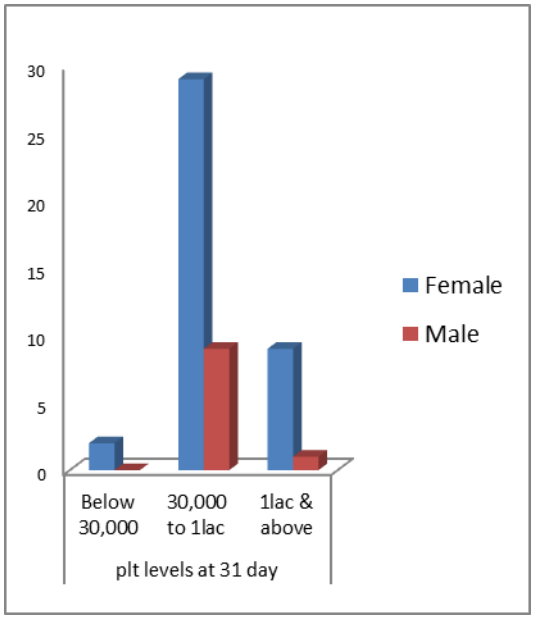
Majority our patients achieved peak platelet levels after third week of treatment. The average plt count before VCR was 4 and peak plt count achieved on an average was 79.2. No response= PLT count ≤30 thousand at day 31 of VCR. Partial response= PLT count 30- 100 thousand at day 31 of VCR. Complete response=PLT count ≥100 thousand at day 31 of VCR.

Figure 3: Platelet response.



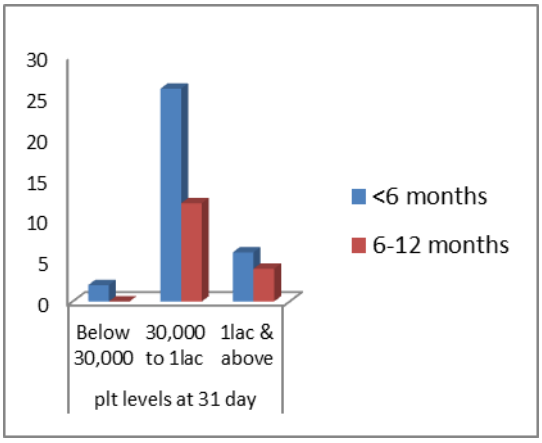
Our study did not show any relation between sex and platelet response to VCR at day 31. Out of all female patients (40), 2(4%) showed no response, 29(58%) were partial responders and 9(18%) showed complete response. In this study we had 10 males out of which 9(18%) showed partial response and 1(2%) showed complete response. This is shown in figure 4

Figure4: Sex and platelet response at day 31



In this study there was no significant relationship between duration of illness and platelet response at day 31.This is showed in figure 5.

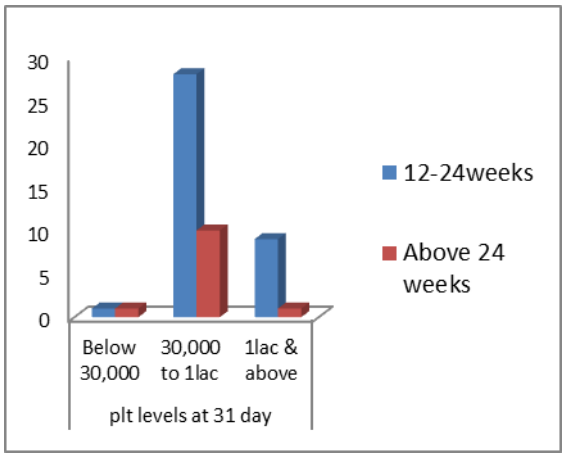
Figure 5: Duration of illness and platelet response at day 31.



Our study showed that there was no significant relationship between duration of steroid use and platelet response to VCR at day 31. Among these patients76% (n=38) who were treated with steroids for 12 to 24 weeks , 2% (n=1) had no response, 56% (n=28)were partial responders and 18% (n=9) had complete response at day 31. Out of 24% (n=12) patients who were treated with steroids for more than 24 weeks, 2% (n=1) was non

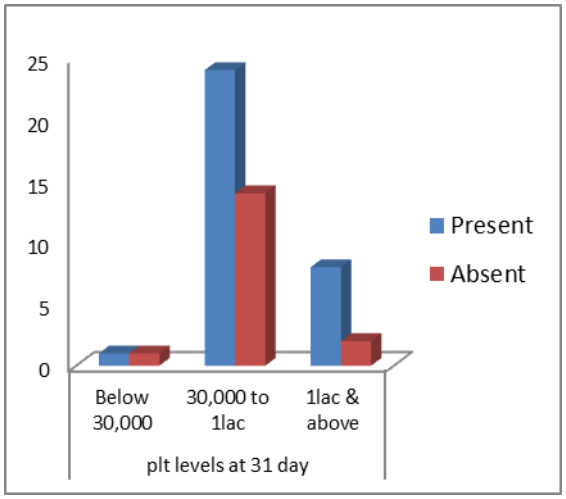
responder, 20% (n=10) were partial responders and 2% (n=1) showed complete response. This is showed in figure 6.

Figure 6: Duration of steroids and platelet response at day 31



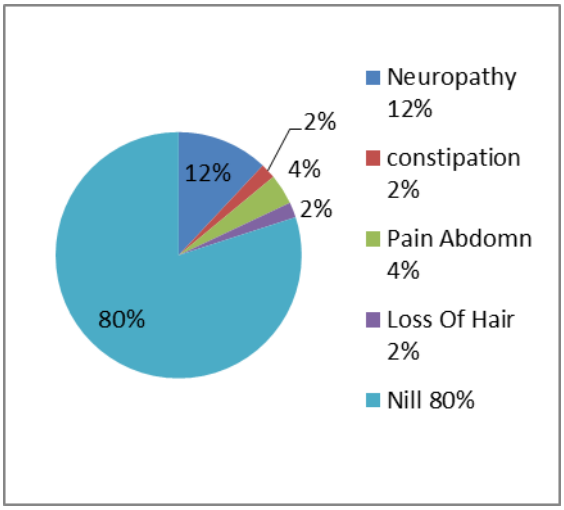
In this study there was no significant relation between presence of signs of bleeding and platelet response to VCR at day 31. The only significant relation was that all patients who received VCR had disappearance of signs of bleeding at day 31.This is shown in figure 8.

Figure7: Signs of bleeding and platelet response at day 31.



In our study 20% (n=10) patients developed various side effects, 80% (n=40) had no side effects at all. Overall12% (n=6) developed neuropathy, 2% (n=1) had constipation, 4% (n=2) developed pain abdomen and 2% (n=1) developed loss of hair. This is shown in figure 8.

Figure 8: Side effects:



V. Discussion

ITP is an autoimmune disorder, as indicated by the presence of IgG-type antiplatelet antibodies in the serum of patients with ITP,which render the platelets susceptible to destruction by the macrophages. Although this is the main mechanism, a possible role of cell-mediated immunity has not been excluded. The benefit of splenectomy would therefore result not only from an increase of the platelet life span by removal of the major mass of macrophages, but from the removal of the main source of antibodies. Corticosteroids act by reducing antibody production, and therefore may be useful in such patients. Corticosteroids and/or splenectomy result in acceptable clinical control in 70 to 90% of all patients. Based on the fact that ITP is generally caused by antibodies, Immunosuppresive agents may be useful in refractory ITP with serious disease, as well as in patients unsuitable for surgery and for corticosteroids because of the fact that ITP is caused by antibodies.Vinca alkaloids have been increasingly used in refractory ITP in the past. These drugs are cytostatic for the macrophages. The Vinca alkaloids bind to tubulin, a structural protein of microtubules. As platelets are very rich in microtubules, they are avid in uptake of Vinca alkaloids. These agents, carried by the platelets go into the macrophages, leading to their dysfunction or death, as a consequence of which medical splenectomy would be produced, which would result in decreasing the platelet clearance as well as the antibody production. Moreover, thrombocytosisis is frequently observed in patients who are treated with Vinca alkaloids for oncological disorders. All these observations suggest that, besides the cytostatic effect, the alkaloids have a second thrombocytopoietic effect. Previous experimental studies in laboratory animals, in which thrombocytosis followed the administration of the Vinca alkaloids, may give support for the latter hypothesis.Thus, 2 independent effects of the drug would act in ITP. This double action of VCR (cytostatic and thrombocytopoietic) therefore would be an advantage as compared to other immunosuppressive agents. [18] In the past several studies have been carried out on the role of vinca alkaloids as second line drug in ITP. In a study carried out by CervantesF et al Eight patients who were

diagnosed as corticosteroid refractory (ITP) were treated with low-dose vincristine (1 mg/week up to a total dose of 4 mg).Complete remission was achieved in 2 cases and partial remission in 3. [18] In a study carried out by Nenci GG et al, Three infusions of VCR-loaded platelets were carried out in a young man with acute ITP refractory to steroids. This procedure insured a remission without side effects. [19] Kueh YK et al,studied 12 patients of chronic steroid refractory ITP who received weekly (1 mg) vincristine injections to a cumulative dose not greater than 3 mg. No complications were encountered. 8 patients (67%) showed a rise in the platelet count following the first injection. 5 out of the 8 patients achieved a normal platelet count (greater than 150 X 10(9)/1) after the second dose of vincristine, while 3 obtained variable platelet rises of 20 to 110 X 10(9)/1 above the pre-treatment levels. [20] Z Gross et al, reported first case of successful vincristine treatment for autoimmune thrombocytopenic purpura in pregnancy.[21] Khalifa AS et al, studied Twenty-four steroid refractory ITP patients with persistent PC < or = 20 x 10(9)/l who received vincristine 1.5 mg/m2/week i.v. 4 doses (n = 4) with no clinical or hematological improvement. [22]I Williams JA et al, studied Ten adolescent patients with ITP refractory to medical management,which included gluco-corticosteroid, intravenous immunoglobulin or anti-Rh (D) IgG, or splenectomy, who were given weekly doses of vincristine 1.5 mg/m intravenous push (IVP) (maximum dose 2 mg), weekly methylprednisolone 100 mg/m IVP, and cyclosporine (CSA) 5 mg/kg orally twice daily. Seven patients acheived continuous complete responses (platelet count normal after cessation of CSA), a median of 13 months (9-37 months) after completion of therapy. One patient had a partial response. Two patients were nonresponders[23] . In our study a total of 50 patients who were diagnosed as ITP and were unsuccessfully treated with steroids were enrolled for this study. All patients received four doses of VCR 1.5mg/ m2/wk I/V push for four consecutive weeks. This was followed by observing platelet response at day 1, day 3 and day 7 each week for four consecutive weeks. This study showed that Out of all female patients (n=40), 4%(n=2) showed no response, 58%(n=29) were partial responders and 18%(n=9) showed complete response. In this study we had 10 males out of which 18%(n=9) showed partial response and 2%(n=1) showed complete response. Overall 4%(n=2) of patients showed no response, 76% (n=38) of patients showed partial response and 20%(n=10) showed complete response. Total number of patients which showed response to VCR including both partial responders and complete responders is 96% which is significantly high and statistically significant (p value≤0.0001). In this study average platelet count before VCR injection was 4 thousand and peak platelet count achieved on an average was79.72. Majority of our patients achieved peak platelet count after third week of treatment that is around day 25. In this study 80% (n= 40) of patients did not have any adverse effects, but 20% (n=10) developed adverse effects. Out of this 12%(n=6) developed neuropathic symptoms, 2%(n=1) developed constipation,4%(n=2) developed pain abdomen and 2%(n=1) developed loss of hair. Our study did not show any relation between age, sex and platelet response to VCR at day 31. In this study there was no significant relationship between duration of illness and platelet response at day 31. Our study showed that there was no significant relationship between duration of steroid use and platelet response to VCR at day 31. In this study there was no significant relation between presence of signs of bleeding and platelet response to VCR at day 31. The only significant relation was that all patients who received VCR had disappearance of signs of bleeding at day 31. Our study highlights the effective role of VCR as second line drug in steroid refractory ITP in our population who do not always afford the very costly alternative regimens.

VI. Conclusion

ITP is an acquired autoimmune disorder defined by a low platelet count secondary to accelerated platelet destruction or impaired thrombopoiesis by antiplatelet antibodies. VCR has a double action (cytostatic and thrombocytopoietic) that would be an advantage as compared to other immunosuppressive agents. Therefore, we suggest an effective, economical and second line role of VCR in steroid refractory ITP.

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I dedicate this work to my father late Mr. manzoor ahmad kana of whom I am a reflection to this world. Special thanks to prof Javid Rasool (H.O.D clinical hematology skims soura j&k), Dr.sajjad Geelani (Associate prof clinical hematology skims soura j&k) for their guidence and well wishes.

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