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Platelet Indices As Markers For Remission In ALL During Induction of Remission: An Experience of 52 Cases

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Abstract

Background: *Platelet indices (plateletcrit, mean platelet volume, platelet distribution width and Platelet count) are potentially useful markers for the early diagnosis and outcome of many diseases. Platelet indices could serve as surrogate marker for remission in patients with ALL.*

Objective: *To observe change of platelet indices in ALL during induction of remission.*

Material & Methods: *This observational study was carried out with 52 newly diagnosed ALL patients ranging from 1.5 to 12 years admitted at DMCH, from January to December 2015. Platelet indices such as plateletcrit (PCT), mean platelet volume (MPV), platelet distribution width (PDW) and platelet count (PLT) were monitored from admission to induction of remission phase of chemotherapy and were analyzed.*

Result: *Mean PLT was found 93442.3±29966.4 cmm before treatment, 137442.3±27217.9 cmm in 1st week and 231653.8±42543.5 cmm in 4th week. Mean PCT was found 0.09±0.11% before treatment, 0.16±0.11% in 1st week and 0.25±0.18 % in 4th week. Both PLT & PCT was increased significantly during induction of remission after one and four weeks. Mean PDW was found 13.1±3.9 fl before treatment, 12.9±3.5 fl in 1st week and 12.0±3.1 fl in 4th week. MPV was found 10.6±2.1 fl before treatment, 11.0±1.4 fl in 1st week and 10.7±1.4 fl in 4th week. The change of MPV & PDW were not statistically significant when compared with that of before treatment.*

Conclusion: *It can be concluded that among four important platelet indices, PLT and PCT were significantly associated with remission in ALL during induction of remission.*

Keywords: *Platelet Indices, ALL (Acute Lymphoblastic Leukemia), markers of induction of remission.*

Introduction:

Leukemia constitutes 25-30% of childhood cancers and ALL constitutes 75-85% of leukemia's. Due to the uncontrolled accumulation of the blasts initially in the bone marrow, the other hematopoietic elements are suppressed. As the disease progresses the excess blasts may spread to blood stream and infiltrate organs and tissues.[1]

The mechanism of bleeding causes by leukemia is complex and involves leukemic cells infiltration in the vessel wall, reduction of platelet production and function. A quantitative reduction and qualitative dysfunctioning of platelets are the leading causes of bleeding in acute leukemia.[2,3] In cancer treatment, treatment of childhood ALL has made a breakthrough. Currently 5-year survival rate has reached 94%.[4]

Platelets are derived from their precursors, the megakeryocytes whose differentiation is characterized by nuclear polyploidization through a

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process called endomitosis and ultimately platelets bud off.[5]

The quantitation of blood cell counts (red cells, white cells, and platelets) is an old and a well-recognized tool. Now a days, new indices related to platelet count have been estimated by automated blood cell analyzers. They help in disease diagnosis in early phases, monitor diseases progression and determine therapeutic outcomes. The most important indices are plateletcrit (PCT), mean platelet volume (MPV), platelet distribution width (PDW) and Platelet count (PLT). PLT reflects the platelet metabolic dynamics in the peripheral blood and often found low in acute leukemia. PCT is calculated by multiplying PLT and MPV. It changes in the direction as PLT does. MPV reflects megakaryocytes proliferation, metabolism, and platelet production in the bone marrow.[6,7]

Newly produced platelets have large volume, higher MPV value and more active function. When platelets decrease in number, bone marrow megakaryocytes are stimulated by thrombopoietin. Platelet activation leads to changes in platelet shape with increase in platelet swelling leading to an increase in MPV.[8,9] Thus, platelets with a higher MPV are expected to be seen in destructive thrombocytopenia when megakaryocytic stimulation is present and there was no statistically significant difference in MPV values among the subtypes of leukemia.[10]

PDW is a more reliable marker for discriminating hyper destructive thrombocytopenia from hypoproductive thrombocytopenia.[11] Moreover, it has been shown that MPV is a reliable measure of residual platelet function in stored platelet concentrate, an increased MPV representing deterioration of the product.[12] High MPV and low PDW were reported in patients with leukemia.[10]

There are inconsistencies in respect to early changes in platelet volume parameters and its clinical implication in acute leukemia. It has been demonstrated that children with leukemia have an abnormally high but not significantly different MPV, whereas PDW was significantly smaller. It is proposed that the use of PDW is an indicator of certain pathological states and to screen leukemia.[10] On the other hand, different subtypes of acute leukemia cannot be differentiated by the use of platelet indices (MPV and PDW).[13]

In early stage of thrombocytopenia, platelet indices signal hematopoietic dysfunctions and its specificity and sensitivity are related to patient's age, processing time of the specimens and so on. In severe thrombocytopenia, the platelet indices limit the range of application because of platelet histogram cannot be drawn and there are obstacles in parameter recording.[14] In clinical practice dynamic monitoring of platelet indices, change is indispensable. In ALL, when chemotherapy is terminated, bone marrow functions gradually restore and significant changes occur. This is important for the assessment of medication efficacy and prognosis. In childhood ALL specially for non-minimal residual disease, concluded that the platelet count after induction therapy can achieve better treatment stratification.[15] Objective of this study was to observe change of platelet indices in ALL during induction of remission.

Materials and Methods:

This was an observational study conducted in the department of Paediatric Haematology and Oncology, Dhaka Medical College Hospital, Dhaka from January 2015 to December 2015. A total of 52 diagnosed case of ALL undergoing induction of remission at inpatient during study period were included in this study. Data were collected by interview, physical & lab examination using a structured questionnaire containing all the variables of interest. Patients with relapse of ALL, ALL with complications and patients in whom standard treatment protocol could not be administered due to any limitation were excluded from the study.

Three to four milliliters of blood were collected by venipuncture into an evacuated tube containing K_3 EDTA (tripostassium ethylene diamine tetraacetic acid) and blood counts were performed within 2 hours of sample collection by Sysmex Automated Hematology Analyzer (Model: XS-500i, made in Japan). The following hematological parameters were then studied in all blood samples: PLT, MPV, PDW and PCT.

Platelet indices were obtained at the time of admission and/or after diagnosis prior to initiation of induction therapy, thereafter, blood sample were collected at first week and fourth week during the induction of remission phase. The variation of

changes among the patients and the changing profile with chemotherapeutic agent were obtained from the data that were recorded in a structured questionnaire and then anlyzed.

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Paired t-test was used for continuous variables. P values <0.05 were considered as statistically significant. Informed written consent was taken from parents or caregiver of each child and ethical approval was taken from hospitals ethical review committee.

Results:

A total of 52 children were diagnosed as ALL. In this study, different platelet parameters were investigated before and after induction of remission to observe whether platelet indices (PLT, PCT, MPV, and PDW) could serve as markers for remission. For this purpose, all patient related data (i.e. demographic variables, clinical features, and investigation and platelet indices) are presented in the following tables.

Table-I

Distribution of the study patients by demographic variable (before treatment) (n=52)

Demographic variable	Number of patients	Percentage
Age (in years)		
<5	20	38.5
5-10	26	50.0
>10	6	11.5
Mean±SD	6.2 ±3.3	
Range (min, max)	1.5 , 12	
Sex		
Male	33	63.5
Female	19	36.5

A total 52 patients were analyzed in this study. Among them 50.0% patients belonged to age 5-10 years and the mean age was being found 6.2±3.3 years. 63.5% patients were male and female were 36.5%. Male female ratio was 1.7:1.

Table II

Baseline clinical characteristics of study patient (before treatment) (n=52)

Presenting complaints	Number of patients	Percentage
Fever	49	94.2
Anaemia	51	98.1
Bleeding	38	73.1
Purpura	17	44.7
Gum bleeding	13	34.2
Other bleeding manifestation	7	18.4
Bruise	1	2.6
No	14	26.9
Clinical presentation	Number of patients	Percentage
Bony tenderness	22	42.3
Lymph node		
Lymphadenopathy	39	75.0
Not palpable	13	25.0
Organomegaly	45	86.5
Spleen palpable	43	82.7
Liver palpable	44	84.6
Both palpable	42	80.8
No organomegaly	7	17.6

Among 52 patients, 94.2% patients had fever and 98.1% patients had anaemia. Bleeding was found in 73.1% patients, among them 44.7% had purpura, 34.2% had gum bleeding, 18.4% had other bleeding manifestation, 2.6% had bruise and in 26.9% cases no bleeding was found. 42.3% of the patients had bony tenderness, 75% lymphadenopathy and 86.5% patients had organomegaly. Palpable spleen was found in 82.7% patients, palpable liver in 84.6% patients and both were palpable in 80.8% patients.

Table III

Distribution of study patient by investigation (before treatment) (n=52)

Investigation	No. of patients	Percentage
Hemoglobin (g/L)		
≤7	9	17.3
7-9	17	32.7
>9	26	50.0
Mean±SD	9.1	±2.6
Range (min, max)	2.3 , 14.6	
WBC count (10^3/µL)		
<10,000	4	7.7
10,000-50,000	2	3.8
>50,000	46	88.5
Mean±SD	25672.4±6455.5	
Range (min, max)	710, 358440	
Platelet count (10^3/µL)		
<100	37	71.2
>100	15	28.8
Mean±SD	93442.3±29966.4	
Range (min, max)	0, 445000	
Bone marrow examination	52	100.0
Leukemic blast count on bone marrow (%)		
25-50	25	48.1
50-75	20	38.5
>75	7	13.5
Immunophenotype		
B Cell	24	46.2
T Cell	6	11.5
Not Done	22	42.3

Before starting treatment initial Hemoglobin was found 9.1±2.6 g/l with ranging from 2.3 to 14.6 g/l, the mean WBC count 25672.4±6455.5 cmm, mean platelet count 25672.4±6455.5 cmm. Bone marrow examination was done in 100.0% patients, 25-50 percent leukemic blast count on bone marrow was found in 48.1% and B cell immunophenotype was found in 46.2% patients.

Mean PLT was found 93442.3±29966.4 cmm before treatment, 137442.3±27217.9 cmm in 1st week and 231653.8±42543.5 cmm in 4th week. Increase of mean PLT at 1st week and 4th week were statistically significant ($p<0.05$) when compared with before treatment.

Mean PCT was found 0.09±0.11% before treatment, 0.16±0.11% in 1st week and 0.25±0.18 % in 4th week. Increase of mean PCT at 1st week and 4th week were statistically significant ($p<0.05$) when compared with before treatment.

Mean PDW was found 13.1±3.9 fl before treatment, 12.9±3.5 fl in 1st week and 12.0±3.1 fl in 4th week. Difference of mean PDW at 1st week and 4th week were not statistically significant ($p>0.05$) when compared with before treatment.

Mean MPV was found 10.6±2.1 fl before treatment, 11.0±1.4 fl in 1st week and 10.7±1.4 fl in 4th week. Difference of mean MPV at 1st week and 4th Week were statistically not significant ($p>0.05$) when compared with before treatment.

Table-IV

Platelet indices before treatment, after 1st week and after 4th week (n=52)

Platelet indices	Before treatment Mean±SD with Range (min, max)	1st week Mean±SD with Range (min, max)	4th week Mean±SD with Range (min, max)	P value
PLT	93442.3±29966.4	137442.3±27217.9	231653.8±42543.5	0.001*
(Platelet count, cmm)	0, 445000	4000, 412000	7000, 526000	
PCT (plateletcrit, %)	0.09±0.11, 0, 0.42	0.16±0.11, 0, 0.44	0.25±0.18, 0.1, 0.72	0.001*
PDW (platelet distribution width, fl)	13.1±3.9, 7.1, 22.2	12.9±3.5, 8.0, 22.2	12.0±3.1, 7.1, 21.2	0.101
MPV (mean platelet volume, fl)	10.6±2.1, 1.6, 16.6	11.0±1.4, 8.2, 14.6	10.7±1.4, 8.2, 14.1	0.644

* = significant

Discussion:

In this study, 20 patients were aged below 5 years, 26 of them with 5 to 10 years and 6 cases are aged above 10 years. It was observed that majority (88.5%) patients belonged to age 1-10 years. The mean age was found 6.2±3.3 years with ranging from 1.5 to 12 years. In a study, out of 77 patients, median age was reported as 9 years (range 1–17 years).[16] Similarly, another study also found that out of 60 patients, median age at diagnosis was 5.9 years (range 1.4–9.3 years).[17] These results are comparable to our current study. In this present study, we found male to female ratio was 1.7:1. It was similar to another study where male to female ratio was 1.25:1 with overall male gender prevalence.[18]

It was observed that most of the (94.2%) patients had fever. Almost all (98.1%) of the patients had anemia. Bleeding was found in 70.6% of patients. Bony tenderness was found in 42.3% patients. Organomegaly was found in 86.5% of patients. Palpable spleen was found in 82.7% patients, palpable liver was 84.6% patients, and both palpable spleen and liver was 80.8%. Biswas S et al. in their study found that common symptoms and signs were fever (85.3%), pallor (64%), hepatomegaly (72%), splenomegaly (60%) and lymphadenopathy (50.7%).[19] Faseeh S et al.[20] found that hepatomegaly in 71% of patients, splenomegaly in 66%, lymphadenopathy in 71% and in 31% of patients all three were enlarged in ALL patients and almost similar findings were reported by Yasmeen N et al.[21] which are consistent with our findings.

Leukemic blast count on bone marrow examination was found in 48.1% patients and B cell immunophenotype was found in 46.2% of patients. Lustosa de et al. also reported that under 19 years of age with newly diagnosed ALL, B-ALL was more common (89.5%) than T- ALL.[22]

This study showed that mean PLT increased at 1st week and 4th week were statistically significant ($p<0.05$) which is consistent with the observation of Balduini Cl et al.[23] In this study we found that mean PCT at 1st week and 4th week were significantly increased which supports that PLT may function as a surrogate marker for an overall poor treatment response to induction treatment with slow clearance of leukemic cells from the bone marrow and the associated compromised hematopoietic recovery.[15]

MPV is calculated from a log transformation of the platelet volume distribution curve, yielding a geometric mean for this parameter[24-26] In our study, no statistically significant difference was found in MPV values between before treatment with different stages of induction of remission. This is probably because MPV depends on the number of new platelets and Sakha K et al. also found that in leukemia there was no meaningful relationship between disease and MPV[27] which is consistent with our present study.

PDW is the SD of the log-transformed data of platelet. It has been reported that PDW increases over storage time because of the formation of abnormally small and large platelets, and PDW is useful as a predictor of the viability of transfused platelets.[28-30] In the current study, we found differences in PDW are not statistically significant. Balduini CL also reported that PDW reflects the heterogeneity with platelet volume and that differences in PDW are not significant.[23]

Conclusion:

Among four important platelet indices, PLT and PCT were significantly associated with the treatment outcome and can be used as markers for predicting remission in ALL. MPV and PDW both do not change significantly at the remission phase in comparison to before treatment.

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