Coagulopathy in Adult Acute Leukemia at Presentation in National Center of Hematology (NCH), Baghdad

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Abstract:

Background: Malignancy is associated with a hypercoagulable state and a high risk for thrombohemorrhagic complications, clinical complications may range from localized thrombosis more in solid tumors to bleeding of varying degrees of severity because of disseminated intravascular coagulation (D.I.C.) as in acute leukemia.

Aim of the study: To search for the real cause of coagulopathy (bleeding or thrombosis) in patients with acute leukemia.

Materials and methods: This study was conducted at the NCH between January 2010 and September 2011, 96 patients with acute leukemia where evaluated prospectively for hemostatic abnormality at presentation of which 43 (44.79 %) had acute lymphoblastic leukemia (ALL) and 53 (55.21 %) had acute myeloid leukemia of which 14 (14.58) were cases of Acute Promyelocytic Leukemia (APL).

Results: At presentation 2 patients (2.3 %) with AML (M3, APL) subtype had bleeding manifestation (signs of intracranial hemorrhage) and died with in 24-48 hours in spite of urgent supportive managements, (94)patients (97.9 %) had variable abnormalities of coagulation indices which include prothrombin time (P.T.) , partial thromboplastin time (P.T.T.), plasma fibrinogen level and Factor VII levels, ranging from normal indices specially in ALL to slight increment in AML mainly M2 to moderate increase in some patients with M3 (bleeding manifestations noticed to be associated more in few AML M3 this was attributed to the procoagulant activity of cytoplasmic granules in the malignant promyelocytes.

Conclusion: From the results obtained in this study which shows that the cause of bleeding is mostly associated with low platelets count , but not due to coagulation factors defects (as only PT was increased in some cases of AML) .

Key words: Acute lymphoblastic leukemia, acute myeloid leukemia, acute promyelocytic leukemia.

Introduction:

Malignancy is associated with a hypercoagulable state and a high risk for thrombohemorrhagic complications [1- 3] , clinical complications may range from localized thrombosis more in solid tumors to bleeding of varying degrees of severity because of disseminated intravascular coagulation (D.I.C.) [4-6] .

Life threatening bleeding is frequent in acute leukemias, particularly in acute promyelocytic leukemia (APL) [4]. An important pathogenetic role is attributed to the leukemic cell properties interfering with haemostatic mechanisms, leukemias present with abnormalities in laboratory tests of blood coagulation, even without clinical manifestations of thromboembolism or hemorrhage, these abnormalities demonstrate different degrees of blood clotting activation and characterizes the so called hypercoagulable state in these subjects [7- 9] In recent years there has been interest in severe DIC frequently complicating the onset of acute leukemia , after a better understanding of the biology of leukemia cells, the improvement in laboratory tests for detecting DIC and to changes in the management of this complication subsequent to new therapies for curing leukemia[4].

The probability of developing severe hemorrhages varies according to the type of acute leukemia and type of therapy, APL (AML M3 subtype) typically presents with life- threatening hemorrhagic syndrome ([4,10]).

The abnormalities of blood clotting system underlying the clinical pictures of coagulopathy in APL include hypofibrinogenemia increased levels of fibrin degradation products (F.D.Ps.), and prolonged prothrombin time and thrombin times [11].

1-The intrinsic procoagulant properties of transformed cells are important pathogenetic factors for the activation of blood coagulation in malignancy which are described as:

a) Tissue factor.

b) Fibrinolytic and proteolytic properties.

c) Cytokine release-TNF –Alfa and IL IB.

2- Other factors as antitumor therapies .

3-Infections contribute to the activation of haemostatic system.

Treatment of coagulopathy remains primarily supportive by aggressive transfusions of platelets and cryoprecipitate with no apparent clear role of heparin usage or antifibrinolytic therapy.[11]

Aim of the study:

This study was conducted to find real cause of coagulopathy between types of leukemia (which may be manifested as bleeding tendency) in patients diagnosed with acute leukemia in NCH .

Material & methods:

All patients presented to our center with suspicion of acute leukemia were investigated thoroughly by doing:

Complete blood picture (C.B.P.) & blood film by taking blood sample (2.5 ml.) of venous blood put in EDTA tube for each patient then CBC done by using automated machine CELL DYN 1700.

Bone marrow aspirate & biopsy done from right iliac bone (posterior superior iliac spine) by using disposable Jamshidi bone marrow needle gage 11*100mm (Hospital service , Italian manufacture) , then bone marrow slides were made directly from the aspirate & stained using leishman stain , sudan black B stain , then these slides were examined for morphological changes to reach proper & final diagnosis (sometimes additional cytochemical stains use to confirm the diagnosis) .

Full coagulation study which include (P.T. , P. T. T., plasma fibrinogen , factor VII estimation) done by taking 2 ml. venous blood sample added to 0.4 ml trisodium citrate 3.2% as anticoagulant and the above procedures done either manually according to procedures described in practical hematology (Dacie & Lewis) or by using automated machine from company Diagnostica Stago model ST ART (serial number A 451052638) from BioRad .

All patients were investigated thoroughly and results were registered to be compared, and then statistically evaluated.

Results:

results are recorded according to patients name, age, sex, findings of complete blood picture, bone marrow diagnosis (type of leukemia), results of coagulation study , analyzed statistically by using T &ANOVA tests as seen in tables1– 5 as seen below:

Table 1 Hemoglobin (Hb) concentration:

Hb concentration	Range (g/dl)	Mean ± S.E. (g/dl)	*P-value
ALL	4.3 – 13.6	8.78 ± 0.37	0.198
AML	4.1 – 15.2	8.4 ± 0.40	
APL and its variant	4.6 – 11.0	8.6 ± 0.79	

* P-value for ALL vs. AML 0.666, P-value for ALL vs. APL 0.217, P-value AML vs. APL 0.189

Table 2 WBC count:

WBC count	Range ($*10^9$/l)	Mean ± S.E. ($*10^9$/l)	**P-value
ALL	1.1 - 224	25 ± 7.36	0.98
AML	0.7 - 288	52.4 ± 12.1	
APL and its variant	1.7 – 74.5	23.5 ± 7.84	

** P-value for ALL vs. AML 0.05, P-value for ALL vs. APL 0.53, P-value AML vs. APL 0.18

Table 3 Platelet count:

Platelet count	Range ($*10^9$/l)	Mean ± S.E. ($*10^9$/l)	**P-value
ALL	3 - 296	59.9 ± 9.7	0.534
AML	7 – 349	68.2 ± 11.7	
APL and its variant	7 - 55	34.2 ± 6.4	

** P-value for ALL vs. AML 0.901, P-value for ALL vs. APL 0.036, P-value AML vs. APL 0.086

Table 4 Peripheral blood blasts (promyelocytes):

Bone marrow blasts	Range (%)	Mean ± S.E. (%)	**P-value
ALL	1 - 95	43.3 ± 5.2	0.035
AML	2 - 96	47.7 ± 5.1	
APL and its variant	10 - 91	45.6 ± 11.6	

** P-value for ALL vs. AML 0.552, P-value for ALL vs. APL 0.856, P-value AML vs. APL 0.865

Table 5 Bone marrow blasts (promyelocytes) :

Bone marrow blasts	Range (%)	Mean ± S.E. (%)	**P-value
ALL	40 - 98	80.8 ± 2.98	0.721
AML	21 - 92	59.6 ± 3.8	
APL and its variant	48 - 95	84.7 ± 6.4	

** P-value for ALL vs. AML < 0.001, P-value for ALL vs. APL 0.557, P-value AML vs. APL 0.007

Table .:

	ALL	AML	APL	P value
Haemoglobin (g/dl)	8.78±0.37	8.4±0.40	8.6±0.79	0.198x
	(4.3-13.6)	(4.1-15.2)	(4.6-11.0)	0.795
WBC ($x10^9$/L)	25.0±7.36	52.4±12.1	23.5±7.84	0.98x
	(1.1-224)	(0.7-288)	(1.7-74.5)	0.114
Platelets count ($x10^9$/L)	59.9±9.7	68.2±1.7	34.2±6.4	0.534x
	(3-296)	(7-349)	(7-55)	0.028*

*Significant using ANOVA test for difference among different means or student-t-test for difference between two independent means at 0.05 level of significance.
-Data were presented as mean±SEM (Range)

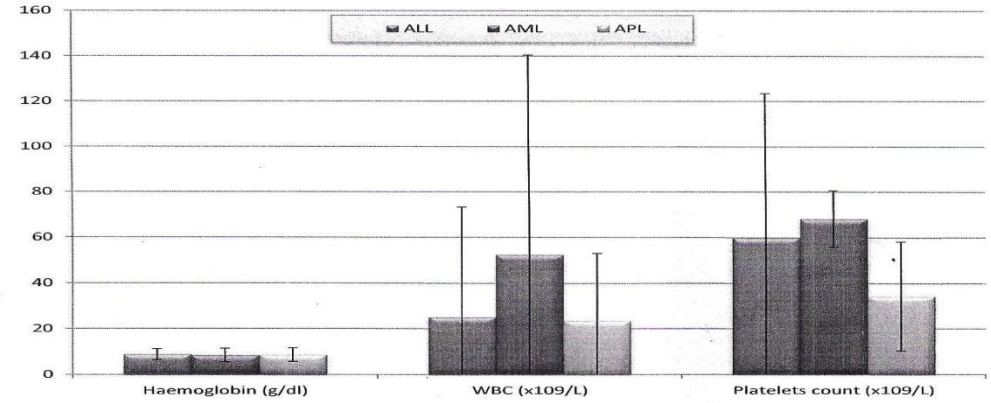

Table .:

	ALL	AML	APL	P value
Peripheral blood blasts	43.3±5.2	47.7±5.1	45.6±11.6	**0.035*x**
(promyelocytes)	(1-95)	(2-96)	(10-91)	**0.844**
Bone marrow blasts	80.8±2.98	59.6±3.8	84.7±6.4	**0.721x**
(promyelocytes)	(40-98)	(21-92)	(48-95)	**0.0001***

*Significant using ANOVA test for difference among different means or student-t-test for difference between two independent means at 0.05 level of significance.
-Data were presented as mean±SEM (Range)

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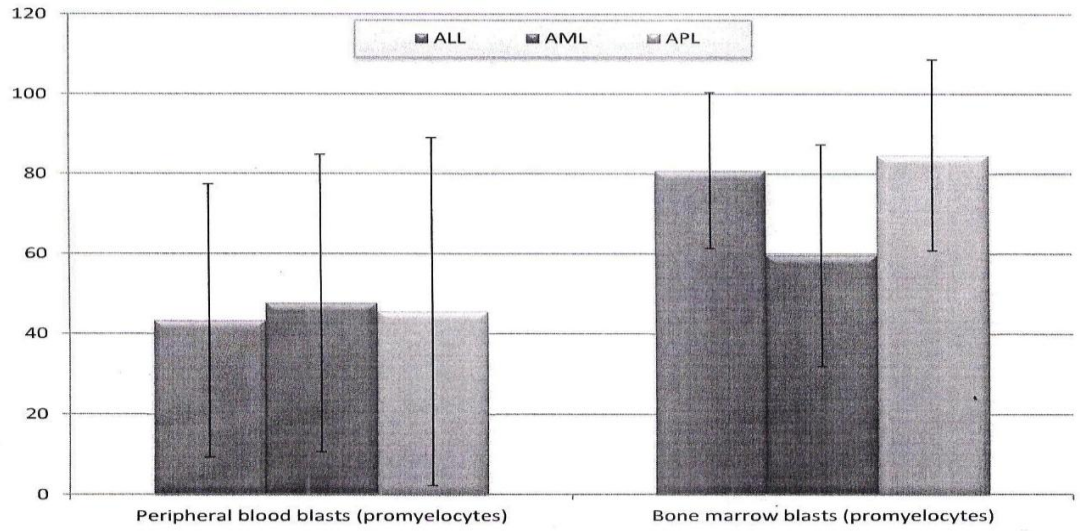

Discussion:

Statistical analysis seen in tables 1 , 2 , 3 , 4 , 5 , in which we noticed no significant relation between hemoglobin concentration , white blood cells counts , platelets counts , in different subtypes of acute leukemia except that platelets counts where there is difference but it is statistically not significant .

There is difference between blasts (promyelocytes in acute promyelocytic leukemia) percentages in bone marrow between ALL & AML but it is statistically not significant.

From what is seen above in our center we notice that the cause of bleeding is mostly associated with low platelets counts , but not due to coagulation factors defects (as only PT was increased in some cases of AML (& M3 specially in 4 / 15 cases) where we thought to be due to factor VII as it had the shortest half life but results of factor VII concentrations were normal in all cases , so what we left to blame for the cause of bleeding is low platelets count which we thought to be the cause &so bleeding stopped when we gave our patients multiple platelets concentrates .

These results goes partially with results published by Dixit A& colleagues [12] where he noticed 85% of patients had thrombocytopenia as a cause of bleeding tendency while 49.3 had some abnormality of global coagulation markers and only two patients shows evidence of DIC .

Recommendations:

Although supplementing patients who had APL with platelets concentrates & fresh frozen plasma (FFP) is an acceptable procedure we noticed that giving platelets concentrate is more appropriate so we advise to use it more frequently.

Encourage blood banking centers to increase number of platelets concentrate bags to patients with acute leukemia & especially those with APL as much as they demand to overcome such bleeding complications.

Monitor patients platelets count carefully to avoid marked thrombocytopenia in such patients & try always to have high platelets count as possible to prevent such bleeding episodes.

References

1. Tiziano Barbui, Falanga A., seminars in thrombosis & hemostasis, volume 27, 2011.
2. Rickles FR, Edwards RL. Activation of blood coagulation in cancer: Trousseau's syndrome revisited. Blood 1983; 62:14–31
3. Falanga A, Rickles F.R. Pathophysiology of the thrombophilic state in the cancer patient. Semin Thromb Hemost 1999; 25:173–182
4. Tallman MS, Kwaan HC. Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. Blood 1992; 79:543–553
5. Barbui T, Finazzi G, Falanga A. The management of bleeding and thrombosis in acute leukemia and chronic myeloproliferative disorders. In: Henderson ES, Lister TA, Greaves MF, eds. Leukemia, 7th ed. Philadelphia: W.B. Saunders; 2001: Chapter 16: 175-199.
6. Barbui T, Finazzi G, Falanga A. The impact of all-trans- retinoic acid on the coagulopathy of acute promyelocytic leukemia. Blood 1998; 91:3093–3102
7. Rickles FR, Levine MN, Edwards RL. Hemostatic alterations in cancer patients. Cancer Met Rev 1992; 11:237–248
8. Falanga A, Barbui T, Rickles FR, Levine MN. Guidelines for clotting studies in cancer patients. Thromb Haemost 1993; 70:343–350
9. Falanga A, Ofosu FA, Delaini F, The hypercoagulable state in cancer: Evidence for impaired thrombin inhibition. Blood Coagul Fibrinolysis 1994; 5:S19–S23
10. Warrell RP, de The H, Wang ZY, Degos L. Acute promyelocytic leukemia. N Engl J Med 1993; 329:177–189
11. Falanga A. Mechanisms for hypercoagulation in malignancy and during chemotherapy. Haemostasis 1998; 28(Suppl. 3): 50–60
12. Dixit A., chatterjee T., Mishra M, choudhry Dr. Mahapatra M., choudhry VP., Saxena R. Disseminated Intravascular Coagulation in Acute Leukemia at Presentation and During Induction Therapy, Clini. appl. thromb hemo .2007 jul, 13 (3) :292-8

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